Evaluating the cost-effectiveness of artemisinin-based combination antimalarial drugs and malaria rapid diagnostic tests within the context of effective vector control:

Case study of southern Africa

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DECLARATION

This Doctoral thesis is my original work and has not been submitted for any academic and/or examination purpose at any other university.

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ABSTRACT

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Evaluating the cost-effectiveness of artemisinin-based combination antimalarial drugs and malaria rapid diagnostic tests within the context of effective vector control: Case study of southern Africa

Abstract:

This study seeks to use the techniques of cost-effectiveness analysis to evaluate, within the context of effective vector control, the change to artemisinin-based combination therapies (ACTs) as first line malaria treatment and to evaluate the relevance of using definitive diagnosis (as opposed to clinical diagnosis) as the basis for initiating malaria treatment, especially when using ACTs for treatment. The cost-effectiveness of ACTs was evaluated in two study sites (i.e. in Kwazulu Natal which switched from SP monotherapy to AL in 2001 and in Mpumalanga which changed from SP monotherapy to AS+SP in 2003) in South Africa. The economic evaluation of use of routine definitive diagnosis as part of malaria case management, using rapid diagnostic tests (RDTs), was undertaken at two districts (Namaacha and Matutuine), in southern Mozambique, where routine use of RDTs and treating malaria patients with an ACT (using artesunate + SP) were implemented at pilot level in 2003.

Data on costs and health outcomes were collected for baseline and post-intervention phases, from a sample of health facilities in the study sites. Costing was undertaken from a public provider's perspective. The evaluation of ACTs in Kwazulu Natal was fraught with methodological challenges because of the impact of the change of treatment policy to ACTs was confounded by the impact of two other malaria control interventions implemented almost at the same time as the ACT intervention. Given this challenge, a Delphi survey was undertaken to estimate the relative contribution of each of the interventions to the improvement in public health outcomes. Further, a decision tree model was used to assess the cost-effectiveness of ACTs so as to allow for better comparison of the different types of ACTs evaluated (i.e. SP monotherapy, artemether-lumefantrine and artesunate+SP).

The key findings from the economic evaluations include:

★ Despite being relatively more expensive, ACTs can be cost-effective. In fact, artemether-lumefantrine and artesunate+SP were not only more cost-effective than SP monotherapy, but also resulted in substantial cost savings in the Kwazulu Natal and Mpumalanga contexts. Results of extensive sensitivity analyses in both Kwazulu Natal and Mpumalanga confirm that ACTs remain cost-effective and cost-saving even when the most conservative values of the key variables (e.g. prices of antimalarials, average length of stay for malaria admissions and

annualisation rates for capital costs) are considered. The finding that ACTs are cost-saving in Mpumalanga is particularly important in two ways:

(a) SP monotherapy was still highly effective in Mpumalanga (90%) unlike in Kwazulu Natal where its effectiveness had declined to only 12%;

(b) There had been no changes in local vector control programme in Mpumalanga (as was the case in Kwazulu Natal); hence the impact of ACTs was not confounded in Mpumalanga.

★ The results from this economic evaluation in Mpumalanga suggest that Delphi estimates were underestimated the "true" effect of ACT (alone) in Kwazulu Natal.

★ Results of the decision tree models show that the cost per malaria patient cured is US$ 118.26 with SP monotherapy and US$ 18.28 with artemether-lumefantrine (AL) in Kwazulu Natal, while in Mpumalanga this was US$ 24.05 with SP monotherapy and US$ 12.05 with artersunate+SP (AS+SP). Results of sensitivity analyses for both the Kwazulu Natal and Mpumalanga models show that the ACTs remain more cost-effective than SP monotherapy even when different values for key variables (including cure rates for the antimalarials, cost of antimalarials, cost of diagnosis, and probability of hospitalisation) are used.

★ The introduction of RDTs is likely to be cost saving when ACTs are implemented, at least in areas of low to moderate malaria transmission intensity and/or if all costs related to malaria treatment (not just diagnostic test and ACT drug costs) are taken into account. Findings showed that even when RDTs cost as much as US$ 0.95 per test, they will be cost-saving if the price of antimalarials being used for treatment is US$ 1.77 (for an adult treatment course of artesunate plus SP) and US$ 2.40 (for an adult treatment course of artemether-lumefantrine), and when up to 29% and up to 52% of the febrile patients are found to be malaria positive and are treated with artesunate plus SP and artemether-lumefantrine, respectively. These results show that the more expensive the antimalarial being used for treating malaria patients is, the more economic sense it makes to restrict antimalarials to those who truly need them.

In conclusion, the cost-effectiveness of ACTs is highly dependent on key factors including: coverage (i.e. proportion of the population who need antimalarials who actually get ACTs), capacity of health infrastructure to implement and monitor use of ACTs and to ensure minimised use of monotherapy drugs, price of ACTs, restriction of ACTs to those definitively confirmed as having malaria, and patients' compliance with treatment regimens. Thus, the broad relevance of the findings of the economic evaluations presented in this thesis to other malaria endemic countries requires very careful consideration of the contexts in which malaria is treated.

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DEDICATION

This work is dedicated to God, my Father. May He bring to full completion that which He has begun in me, to the Glory of His Name. May this work accomplish the purposes for which it has been sent and may I remain a ready tool in His Hand to be used for His service according to His will and purpose. All Glory and Honour to you, Lord. Thank you.

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ACRONYMS

ACT	Artemisinin-based Combination Therapies
AL	artemether-lumefantrine
AS	Artesunate
AS+SP	artesunate plus Sulphadoxine-Pyrimethamine
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CPIX	Consumer Price Index (X category)
CQ	Chloroquine
DDT	Dichlorodiphenyltrichloroethane
DoH	Department of Health
EIR	Entomological Inoculation Rate
FMS	Financial Management System
ICER	Incremental cost-effectiveness ratio
IPD	Inpatient Department
IRS	Indoor Residual Spraying
KZN	Kwazulu Natal
MCP	Malaria Control Program
MPUM	Mpumalanga
MRC	Medical Research Council
OPD	Outpatient Department
PHC	Primary Health Care
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
SEACAT	South East African Combination Antimalarial Therapy
SP	Sulphadoxine-Pyrimethamine
US $	United States Dollar
UTL	Useful Therapeutic Life
WHO	World Health Organisation
WTP	willingness-to-pay
ZAR	South African Rand

EXECUTIVE SUMMARY

Malaria is a complex disease that varies in epidemiology and public health impact in different parts of the world Malaria, together with Tuberculosis and AIDS are ranked as the biggest killers in the world and are responsible for a substantial proportion of disease burden to the human race, in terms of morbidity and mortality (all three responsible for nearly 3.7 million deaths in 2001). Estimates by the World Health Organisation indicate that there are 350–500 million clinical cases of malaria each year. These figures may be a significant under-estimate of the true malaria toll considering that the greatest impact of malaria occurs in areas where surveillance systems are weak. On the other hand, however, it is possible that these statistics are grossly over-estimated given that the areas where the greatest proportion of malaria cases occur rely on clinical diagnosis of malaria which can be an overestimate, as these often include many other acute febrile illnesses. Malaria is considered to be endemic in 107 countries, and the prevalence of malaria has been increasing alarmingly, particularly in Africa The health and economic burden of malaria is massive globally, and particularly in sub-Saharan Africa. In sub-Saharan Africa, the world's most affected region, malaria-related illnesses are estimated to claim the lives of 1 million children every year. Moreover, up to 90% of the estimated 350-500 million new clinical malaria cases per year occur in this region. The gigantic burden of malaria to an individual, a household and the entire country – in the short- and long-term – results in health, social and economic costs. In addition to prevention and treatment costs, malaria is associated with over-burdened health systems, treatment seeking costs, lost productivity, retarded physical and cognitive development in children, other neurological sequel, and retarded economic growth through reduced tourism and business investment and an incapacitated labour force. Malaria is estimated to cause a 1.3% reduction in annual per capita economic growth rate of malaria endemic countries. The burden of this disease is particularly felt by the poor and the vulnerable, usually residing in the rural areas with poor access to health services

Malaria control efforts world-wide are focused on several approaches including: vector control (i.e. targeting the control of the mosquitoes that transmit malaria through widespread use of

indoor residual insecticide spraying (IRS) and insecticide treated bed nets (ITNs)), minimising the number of infective bites (especially through bed net use), ensuring early diagnosis and effective treatment, and preventing malaria in high risk groups through intermittent presumptive / preventive treatment or chemoprophylaxis. Early effective treatment and vector control are the key components of malaria control. In view of the fact that global eradication of the anopheles mosquito is not feasible, integrated approaches including vector control, use of insecticide-treated bed nets and effective treatment have been recommended. However, their successful implementation has been severely hampered by various obstacles, including, constrained budgetary resources, the emergence and spread of resistance to antimalarials and insecticides, inadequate health services infrastructure, cultural beliefs and practices, and poor coordination and collaboration amongst malaria control initiatives.

Although malaria control strategies that focus on improving medical treatment for infected people are emphasised, malaria case management has been compromised by resistance to widely available cheap antimalarials, chloroquine (CQ) and more recently, sulphadoxine-pyrimethamine (SP) and amodiaquine (AQ). Antimalarial drug resistance has now become the greatest challenge facing malaria control all over the world. Resistance to Chloroquine was first discovered in South East Asia and South America in the late 1950s and is now widespread in at least 80% of the 92 countries where malaria continues to be a major killer. Resistance to other drugs (e.g. amodiaquine and SP) follows a similar pattern and is becoming widespread, while resistance to drugs such as mefloquine has started developing in SE Asia. Typically, consequences of resistance have serious cost implications and result in the overburdening of weak health care systems, especially for highly endemic and yet poor sub-Saharan African countries. Most of these implications are in the form of higher costs resulting from increases in morbidity rates, prolonged illness and hospitalisation, additional laboratory tests, as well as the use of more expensive second- and third-line drugs. Furthermore, there are costs accrued by the patients and/or their households, in the form of treatment seeking (travel costs) and lost income due to time away from work. Resistance to antimalarials raises a two-fold global concern. Firstly, the pace at which resistance is developing is faster than the pace at which new antimalarial drugs are being developed and

secondly, newly developed antimalarials usually become successively more expensive than the traditional antimalarials, hence becoming 'unaffordable' for the countries that need them the most. More recently, however, there has been a trend towards newer artemisinin-based combinations being relatively cheaper than the artemisinin derivatives presently on the market, although none are nearly as cheap as the widely used monotherapies, chloroquine and sulfadoxine-pyrimethamine. These two concerns underscore the need to find strategies that delay the emergence and curbing the rapid spread of resistance to affordable antimalarials.

Recently a new strategy, the use of antimalarials in combination, has received considerable attention and is now strongly recommended by the World Health Organisation as the most favourable option for treatment of uncomplicated falciparum malaria. Combination therapies, in particular artemisinin-based combination therapies (ACTs), are now widely recommended and increasingly subsidised internationally, to address the public health crisis resulting from widespread antimalarial resistance. ACTs offer the advantages of providing rapid and effective cure, decreasing gametocyte carriage (the stage of the malaria parasite lifecycle responsible for malaria transmission) and thus reducing malaria transmission, and delaying antimalarial drug resistance.

Despite their ability to improve malaria health outcomes, the acquisition cost and affordability of ACTs continue to be a key area for policy debate for countries that are considering their use, particularly those in Sub-Saharan Africa. The prices of artemisinin-based combinations are estimated to be at least 10 times higher than the price of most antimalarials currently used for first line treatment (e.g. CQ, AQ and SP). The trade off between achieving improved health outcomes through a more effective drug and having to buy antimalarials at a relatively higher price requires careful evaluation in any context. The need to assess whether ACTs are cost-effective, in spite of their relatively high prices, motivated the economic evaluation studies, conducted in Kwazulu Natal and Mpumalanga Provinces in, South Africa, that are presented in this thesis.

Artemether-lumefantrine was implemented as treatment policy in Kwazulu Natal in response to the 1999/2000 malaria epidemic, which was fuelled by high levels of resistance to SP. Findings of these studies conducted in Kwazulu Natal show that despite being relatively more expensive, ACTs can be cost-effective. In fact, artemether-lumefantrine was not only more cost-effective than SP monotherapy, but also resulted in substantial cost savings in the Kwazulu Natal context. Between 2000 and 2002, there was a 93.7%, 90.8% and 95% decline in malaria outpatients, malaria inpatients and malaria deaths, respectively, following the implementation of integrated malaria control interventions of strengthening vector control and implementing a highly effective ACT malaria treatment policy. These improved health outcomes translated into cost savings of US$ 205,114 at outpatient level (i.e. an 88.9% reduction in malaria outpatient costs) and US$ 297,193 at inpatient level (i.e an 89.3% reduction in malaria inpatient costs), calculated from the sample of 10 public sector health facilities studied in one sub-district.

However, in the Kwazulu Natal study site, three malaria control interventions of strengthening vector control in Kwazulu Natal, introducing vector control in neighbouring southern Mozambique and introducing an ACT policy, that were implemented in rapid succession, made attributing reduced malaria morbidity and thus costs to ACT alone difficult. Although such an integrated approach is clearly optimal for reducing malaria morbidity and mortality, there is great interest in an estimate the contribution of ACTs alone to the decline in malaria burden and costs in areas where it is not immediately feasible. This need led to the conduct of a Delphi survey. Results from the Delphi survey, calculated from the estimates by 9 malaria experts, showed that the ACT intervention alone is believed to have been responsible for 36%, 46% and 62% of the observed decline in malaria cases, admissions and deaths, respectively. Using these Delphi estimates, ACTs are still found to be cost-saving. Results show that malaria outpatient costs would have declined by 31.8% in Kwazulu Natal, between 2000 and 2002, (i.e. cost saving of US$ 73,343) directly as a result of only changing the malaria first line treatment policy from SP monotherapy to an ACT (i.e. even in the absence of other malaria control interventions). The finding that ACTs are cost-effective and cost-saving holds even if the most conservative estimates of the relative contribution of the change in

drug regimen are used, and if the highly inflated prices of SP paid by Kwazulu Natal are replaced with international median prices.

Given the uncertainty around the extent to which the cost savings realised in Kwazulu Natal were attributable to dramatically improved cure rates and decreased gametocyte carriage associated with using an ACT, an economic evaluation of another ACT was undertaken in Mpumalanga Province, South Africa. The results of economic evaluation in Mpumalanga were compared with those from Kwazulu Natal study site. Interestingly, the change to an ACT, artesunate plus SP, in Mpumalanga has also been found cost-saving. Results from Mpumalanga show cost savings of US$ 69,174 at outpatient level (i.e. a 66.3% reduction in malaria outpatient costs) and US$ 1,035,141 at inpatient level (i.e. a 93% reduction in malaria inpatient costs), calculated from the sample of 34 public sector health facilities studied. This means that use of ACTs in Mpumalanga has the potential for greater cost-savings if the entire province is taken into consideration. This finding that ACTs are cost-saving in Mpumalanga is particularly important in two ways: firstly, SP monotherapy was still highly effective in Mpumalanga (90%) unlike in Kwazulu Natal where its effectiveness had declined to only 12%; secondly, there had been no changes in local vector control programme in Mpumalanga (as was the case in Kwazulu Natal). The results from this economic evaluation in Mpumalanga suggest that Delphi estimates were underestimated the "true" effect of ACT (alone) in Kwazulu Natal. Results of extensive sensitivity analyses in both Kwazulu Natal and Mpumalanga confirm that ACTs remain cost-effective and cost-saving even when the most conservative values of the key variables (e.g. prices of antimalarials, average length of stay for malaria admissions and annualisation rates for capital costs) are considered. These cost savings in both Kwazulu Natal and Mpumalanga resulted primarily from the decrease in the total number of malaria cases and the number of malaria hospital admissions, (i.e. from improved clinical cure rates and decrease in malaria transmission) achieved with the use of artemether-lumefantrine and improved vector control (in Kwazulu Natal) and with the use of AS+SP as first line malaria treatment in Mpumalanga.

The cost-effectiveness of ACTs is confirmed when a decision tree model, which combines the impact of ACTs on both morbidity and mortality, is used in Kwazulu Natal and Mpumalanga. Results of the decision tree models show that the cost per malaria patient cured is US$ 118.26 with SP monotherapy and US$ 18.28 with artemether-lumefantrine (AL) in Kwazulu Natal, while in Mpumalanga this was US$ 24.05 with SP monotherapy and US$ 12.05 with artersunate+SP (AS+SP). Results of sensitivity analyses for both the Kwazulu Natal and Mpumalanga models show that the ACTs remain more cost-effective than SP monotherapy even when different values for key variables (including. cure rates for the antimalarials, cost of antimalarials, cost of diagnosis, and probability of hospitalisation) are used.

One way of promoting more rational use of antimalarials is to restrict the use of antimalarials to only those who need them by relying on routine definitive diagnosis before providing treatment. Treatment of malaria in South Africa is initiated after definitive diagnosis (by microscopy or a rapid diagnostic test), unlike most other malaria endemic countries where malaria is clinically diagnosed. Therefore, the cost-effectiveness of ACTs in these sites is possibly enhanced by the fact that the use of antimalarials is restricted to only those who definitely need them (i.e. after diagnostic test confirmed malaria). Uncertainty around the extent to which definitive diagnosis (primarily using RDTs) contributed to cost effectiveness of ACTs in both Kwazulu Natal and Mpumalanga, which is even more uncertain in areas of higher intensity of malaria transmission, led to the exploration of the cost effectiveness of introducing RDTs as the basis for treatment with ACTs in 15 public healthcare facilities in southern Mozambique. The use of routine definitive diagnosis as part of malaria case management, using rapid diagnostic tests (RDTs), has been found to be cost-effective (and cost-saving in some instances) in the southern Mozambique context. The findings of this study show that the introduction of RDTs is likely to be cost saving when ACTs are implemented, at least in areas of low to moderate malaria transmission intensity and/or if all costs related to malaria treatment (not just diagnostic test and ACT drug costs) are taken into account. Findings from the evaluation of cost-effectiveness of RDTs showed that even when RDTs cost as much as US$ 0.95 per test, they will be cost-saving if the price of antimalarials being used for treatment is US$ 1.77 (for an adult treatment course of artesunate plus SP) and US$ 2.40 (for an adult treatment course of artemether-lumefantrine), and when up to

29%and up to 52% of the febrile patients are found to be malaria positive and are treated with artesunate plus SP and artemether-lumefantrine, respectively. These results show that the more expensive the antimalarial being used for treating malaria patients is, the more economic sense it makes to restrict antimalarials to those who truly need them. Further, results show that limiting the use of RDTs to patients who are over 6 years of age results in lower *additional* costs and/or higher *cost savings* compared to when RDTs are used in all suspected malaria cases as the basis for treatment with an ACT. As long as the unit price of RDTs is similar to or greater than the unit price of antimalarials for treating a child 6 years or younger, restricting the use of RDTs to patients older than 6 years is more cost saving and/or cost-effective than using RDTs in all fever patients. Results of the sensitivity analyses showed that the cost-effectiveness of RDTs is largely dependent on the prices of antimalarials, the price of the RDTs and the age distribution of the febrile patients being tested and proportion of those requiring treatment for malaria. Findings show that the higher the price of the antimalarial used for treatment, and/or the lower the price of RDTs used for routine diagnosis, the more cost-effective (cost-saving) the use of RDTs will be. This economic evaluation did not consider the costs associated with the treatment of the malaria test negative cases, and assumed that healthcare workers would limit ACT treatment to only those that were diagnostic test positive.

Cost-effectiveness of ACTs is highly dependent on key factors including: coverage (i.e. proportion of the population who need antimalarials who actually get ACTs), capacity of health infrastructure to implement and monitor use of ACTs and to ensure minimised use of monotherapy drugs, price of ACTs, restriction of ACTs to those definitively confirmed as having malaria, and patients' compliance with treatment regimens. Thus, the broad relevance of the findings of the economic evaluations presented in this thesis to other malaria endemic countries requires very careful consideration of the contexts in which malaria is treated. In addition, ACT should be co-formulated or at least co-packaged to improve compliance and minimise the use of monotherapy. The extent to which these therapies sustain decreased malaria transmission and limit antimalarial resistance will be critical in determining their longer term cost effectiveness and public health benefits.

1. INTRODUCTION

1.1: BACKGROUND

Malaria, together with Tuberculosis and AIDS are ranked as the biggest killers in the world and are responsible for a substantial proportion of disease burden to the human race (all three responsible for nearly 3.7 million deaths in 2001) [1]. About 2 billion people (more than a third of the world's population) are estimated to live in malaria-endemic areas [2]. Estimates by the World Health Organisation indicate that there were 350 - 500 million malaria cases worldwide in the year 2004, of which 1.1 – 1.3 million people died from the disease [3]. Children and pregnant women in sub-Saharan Africa are the main victims of acute malaria attacks. Malaria is mainly endemic in developing countries that are already struggling with poverty and other poverty-related problems such as inadequate health care services and lack of proper sanitation. Up to 90% of the world's 300 million annual malaria cases and up to 97% of the more than 1 million annual deaths occurred in sub-Saharan Africa [4]. In 2000, malaria was estimated to be the cause of the loss of nearly 45 million disability-adjusted life years (DALYS) – 13% of all DALYS attributable to infectious diseases [5]. Malaria poses an enormous disease burden both in terms of morbidity and mortality, as well as in terms of the economic impact it imposes on malaria sufferers, their households and their governments [2, 3, 6-9]. For instance, Sachs and Malaney argue that "*Malaria short-term costs alone are likely to result in economic losses of several percent of GDP in a single year. ... [Malaria] burden of disease increases over time as countries are deprived of the rise in living standards that they would experience if not for malaria*" [9]. Guerin and others report that estimates of the economic burden of malaria measured in terms of lost opportunity for economic growth range from 0.25% to 1.3% of a country's growth rate of Gross National Product (GNP) per capita [2].

Malaria is a complex disease that varies in epidemiology and clinical manifestation in different parts of the world [10]. Several factors are responsible for the differences in malaria

epidemiology, including among others: climate and other environmental conditions, the species of malaria that occurs in a given area, the effectiveness of drugs used for first line treatment of uncomplicated malaria, and the proportion of the population that has acquired immunity. In view of these differences, malaria control strategies adopted in different regions vary to fit the patterns of malaria prevalence and transmission and the level of resources available for malaria control. The control measures promoted to reduce malaria infection are based on the understanding of the roles of individuals and communities in the transmission, diagnosis, treatment and prevention of the disease [3]. In general, there is strong international advocacy for an integrated approach to malaria control. Such an approach would include prompt and accurate diagnosis, use of effective drugs, effective vector control (through widespread indoor residual insecticide spraying (IRS) and insecticide treated bed nets (ITNs)), reducing the risk of mosquito bites through use of insecticide-treated bed-nets, and prophylaxis or intermittent preventive / presumptive treatment (especially among pregnant women and young children) [11]. Attempts toward world-wide implementation of such an integrated approach have been hindered by several obstacles. One of the major obstacles is the emergence and spread of resistance to residual insecticides and to antimalarials, which has hampered effective vector control and case management efforts. Malaria-related morbidity and mortality have been increasing in sub-Saharan Africa, primarily as a result of increased resistance to the traditional first line treatments, chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) [12, 13]. Antimalarial drug resistance has now become the greatest challenge facing malaria control all over the world [10].

"*Antimalarial drug resistance is the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, ...*" [14, p.8]. Resistance of *plasmodium falciparum* (the commonest malaria parasite) to antimalarial drugs has become a widespread problem in many countries and it is one of the major concerns of governments in malaria endemic countries [15, 16]. In spite of the hindrances posed by widespread antimalarial resistance, prompt diagnosis and treatment of malaria remains the most fundamental and most widespread measure of malaria control globally. In fact, today WHO recommends that

"*access to disease management should be seen not only as a component of malaria control but a fundamental right of all populations at risk. As such, it must be an essential part of health care development*" [3, p.14].

The truth is that the malaria parasite will eventually develop resistance to any drug currently in use and even those that will be developed. Moreover, the, newly developed antimalarials are several times more expensive than the traditional monotherapy antimalarials that were once widely used. Certainly, this poses a challenge for countries in sub-Saharan Africa, which face the highest malaria burden while also facing severely constrained national budgets. The overuse and misuse of antimalarials are believed to play a major role in the emergence and spread of resistance [17-19]. Other factors that influence the development and spread of antimalarial resistance include: poverty and inadequate access to quality drugs; misdiagnosis and self-medication; availability of counterfeit and poor-quality drugs; international travel; poor prescribing practises and poor compliance [19].

Considering that effective malaria treatment is fundamental and integral to malaria management and control, it becomes imperative to focus on finding interventions that are capable of delaying the onset and curbing the rapid spread of resistance to antimalarials. Failure to find such interventions will result in an endless cycle of drug replacement and its associated escalating costs. This problem is of major concern given that most of the relatively expensive antimalarial drugs are in any case not within the reach of many developing countries, as first line treatment. Until recently, only chloroquine (CQ) and/or sulphadoxine-pyrimethamine (SP) are widely used for first line therapy in sub-Saharan Africa. Chloroquine resistance is already widespread with high levels of treatment failure [14]. Although SP was introduced much later (compared to CQ) in Africa as first line treatment, resistance to SP and treatment failure associated with its use are already prevalent and are expected to increase rapidly [20, 21]. Such findings make it essential for governments and international institutions, engaged in the fight against malaria, to find cost-effective strategies that not only delay the emergence of resistance but also continue to provide effective treatment.

Recently a new strategy, the use of antimalarials in combination, has received considerable attention and is now recommended by the World Health Organisation as the most favourable option for treatment of uncomplicated falciparum malaria [3]. "*Combination therapy with antimalarials (CT) is the simultaneous use of two or more schizonticidal drugs with independent modes of action and different biochemical targets in the parasite*" [14, p.17]. Lessons from the treatment and management of TB and HIV have revealed that combining two or more drugs not only provides effective treatment, but also minimises the chances of the emergence of resistance to any one of the drugs in the combination [22, 23].

The strategy of using artemisinin-based combination antimalarials for the treatment of uncomplicated malaria has recently become strongly recommended. Artemisinin-based combination therapy (ACT) is an antimalarial combination with an artemisinin derivative as one component of the combination [14]. Unlike other antimalarials, artemisinins have been shown to directly reduce malaria transmission by decreasing gametocytes. In addition to rapid and effective treatment of malaria, artemisinin-based combination therapy (ACT) has been shown to improve cure rates, decrease malaria transmission and delay antimalarial resistance on the northwest border of Thailand [24]. Improved cure rates and decreased gametocyte carriage have been confirmed in clinical trials of ACTs in Africa [25, 26]. Furthermore, these combination antimalarial therapies have been found to be cost effective in some contexts [27].

There is growing international consensus that wide-scale, systematic implementation of ACT is one of few effective measures that will enable malaria endemic countries to achieve the ambitious goals set in Abuja in 2000 to "Roll Back Malaria", particularly that of halving malaria morbidity and mortality by 2010. The World Health Organisation (WHO) explicitly recommended "*the use of Artemisinin based combination therapy" in order to "provide effective treatment against malaria and to slow the spread of drug resistance*" in a statement released on 20 February 2001. Despite their ability to improve malaria health outcomes, the cost and affordability of ACTs continue to be a key area for policy debate for countries considering their use, particularly those in Sub-Saharan Africa. This trade off between achieving improved health outcomes through a more effective drug and having to buy antimalarials at a relatively higher price requires careful evaluation to ascertain whether the

additional resources spent are 'buying' a 'reasonable' amount of health outcomes. It is important to add, however, that in addition to cost-effectiveness of the antimalarials, there are other factors that are considered in the decision-making process of changing antimalarial treatment policy. Such factors include ease of drug administration, adherence and compliance issues, the safety of the drug, whether the drug can be used in vulnerable target groups such as children and pregnant women and in the case of combination therapies, whether the tablets are co-formulated, co-packaged or not. In instances where the cost and/or cost-effectiveness of the alternatives being considered are similar, then other criteria (not relating to cost) become increasingly important in decision-making.

Generally the acquisition cost of ACT is considerably higher than that of monotherapy drugs. The prices of artemisinin-based combinations are estimated to be at least 10 times higher than the price of most antimalarials currently used for first line treatment (e.g. CQ and SP) [14, 15]. In addition to the direct costs of acquiring combination drugs, implementation costs (including re-training of health workers, printing of new treatment guidelines, withdrawal and disposal of previous drug) need to be taken into consideration in the evaluation of ACTs. However, it is probable that the relatively cheap antimalarials (SP and CQ) could potentially be more 'costly' in terms of their indirect costs associated with treatment failure (e.g. through the need for re-treatment, treatment with second line drugs and hospitalisation, as well as loss of productivity). Clearly, there is need for an evaluation of the affordability and cost-effectiveness of ACTs in countries that are considering changing to them from the traditional first line malaria therapies. Information about cost-effectiveness of ACTs is of particular importance for malaria hyper-endemic countries, which, unfortunately, are also those faced with severe resource constraints. Although the undertaking of an economic evaluation does not replace decision-making, the results of such evaluations would be very helpful in guiding the decision-making process. Some of the key questions that would be addressed by this study include: *What are the 'indirect' costs associated with use of an ineffective antimalarial? Would the use of more effective but more expensive drugs (ACTs) result in cost-savings or additional costs? Are ACTs more cost-effective than the traditional antimalarials (such as CQ and SP)?*

A critical component of effective management of malaria cases and cost-effectiveness of antimalarials is the issue of prompt and accurate diagnosis. Currently, there is heavy reliance on clinical diagnosis in most malaria endemic countries. In the past, clinical diagnosis was justified on grounds that the cost of definitive diagnosis was relatively high compared to the cost of a treatment course of malaria (with cheap drugs such as chloroquine and SP). Indeed Goodman et al., demonstrated, using economic modelling, that despite the low predictive values for clinical diagnosis, the use of additional diagnostic technology was very unlikely to be cost-saving in sub-Saharan Africa because of the use of relatively inexpensive antimalarials at that time (1999) [27]. In addition, without malaria control interventions (such as widespread indoor residual insecticide spraying and use of Insecticide-treated nets/materials), malaria prevalence was high. Hence it made less economic sense to use definitive diagnosis that is more expensive than the drugs used for treatment. Reliance on clinical diagnosis results in misdiagnosis and over-diagnosis of malaria, whereby the malaria diagnosis may be missed in some people needing malaria treatment and those not needing treatment (as their symptoms are caused by diseases other than malaria) are given antimalarials unnecessarily. The recent global focus on the need to effectively reduce the burden of malaria through integrated approaches including: vector control (through IRS and ITNs) and improved early, effective case management; has resulted in reduced transmission of malaria, in areas where such integrated approaches have been implemented successfully. With the increasing need to use more expensive antimalarials (e.g. ACTs) due to antimalarial drug resistance and declining malaria transmission in some contexts, the need for ensuring rational use of antimalarials becomes of paramount importance. One way of promoting more rational use of antimalarials is to restrict the use of antimalarials to only those who need them by relying on routine definitive diagnosis before providing treatment.

The rationale for this study, therefore, is to establish whether the implementation of ACTs is a desirable option in the South African and other African settings; and secondly, to investigate the factors influencing the cost-effectiveness of using definitive diagnosis (using rapid diagnostic tests – RDTs) to limit the use of ACTs.

Traditionally, economic evaluations in health care are conducted to establish whether an intervention is worth implementing. Economic evaluations involve the identification, measurement, valuation and comparison of ***costs*** and ***health outcomes*** of two or more health care interventions [28-32]. Findings of such economic evaluations are intended to guide policy makers in making informed decisions about efficient allocation of resources [28-30, 33, 34].

Although economic evaluation results are increasingly being used to guide decision-making in the allocation of health care resources [35], debates around the limitations of the methodologies employed in these evaluations continue [33, 34, 36-44]. Despite their limitations, however, and in some instances the lack of broad agreement on methodologies, economic evaluations remain useful tools for guiding informed decision-making in resource allocation. It is for this reason that attempts are continually made to refine the methodologies as the awareness and consensus on the need to 'standardise' the application of different methodological techniques grows, in order to ensure comparability and generalisability of results from these evaluations [32-34].

The economic evaluations of artemisinin-based combination therapies presented in this thesis have been undertaken in South-Eastern Africa as part of a large long-term study. The *South-Eastern Africa Combination Antimalarial Therapy* (SEACAT) Evaluation, which commenced in 2000, was designed to comprehensively evaluate the feasibility and impact of artemisinin-based combination therapies as first line therapies in Mozambique, South Africa and Swaziland. The SEACAT evaluation includes studies to monitor therapeutic efficacy of ACTs, molecular markers of resistance, gametocyte carriage, drug safety, treatment seeking, drug utilisation (especially drug availability and patient adherence), distribution and intensity of malaria transmission and the costs and cost effectiveness of implementing ACTs. As part of the overall SEACAT evaluation, the economic evaluation component was designed to assess whether the change from SP monotherapy to artemisinin-based combination therapy is 'cost-effective' in the southern African context where, following widespread deployment of an effective IRS vector control programme, malaria transmission is low and unstable.

Specifically, cost-effectiveness analyses were conducted to evaluate first line treatment options in all the SEACAT study sites (in Mozambique, South Africa and Swaziland). The results presented in this thesis are based on economic evaluations undertaken in only 4 study sites, namely Kwazulu Natal and Mpumalanga provinces (in South Africa) and Namaacha and Matutuine (in Mozambique). Economic evaluations for other SEACAT study sites have not been included in this thesis because of the timing at which the change to ACTs was effected in those study sites. Given the delays in the implementation of the new treatment policy (i.e. ACTs) in some study sites and the need to undertake analyses within a specific timeframe (for the sake of the completion of this thesis), the findings from other study sites have not been included here. However, extensive sensitivity analyses have been undertaken with the data from the study sites considered for this thesis, to allow for the assessment of the impact of variation in key factors that might have been different in other SEACAT study sites.

1.2: RESEARCH PROBLEM

The emergence and rapid spread of resistance to chloroquine and other cheap antimalarials in many parts of the world has become a major global concern, and the limited number of antimalarial drugs available has led to increasing difficulties in the provision of prompt and effective treatment to all who need it [3, 45]. A recent World Health Organisation report documents the existence of resistance of *Plasmodium falciparum* (the most common malaria parasite) to most antimalarials (including chloroquine, amodiaquine, SP and mefloquine) with the possible exception of the artemisinins [3]. Levels of resistance to each drug varies in different countries / areas, but chloroquine resistance is widespread [45]. A wide range of factors including use and misuse of antimalarials, malaria parasite and the human host dynamics are responsible for the emergence and spread of resistance to antimalarials.

A change in first line treatment is usually warranted when resistance to a drug becomes 'unacceptably high'[1]. Unequivocally, the antimalarial chosen to replace an ineffective first line

[1] There is no fixed point of the percentage of clinical failures that should warrant policy treatment change. WHO (2005) recommends that the decision be country-based, but indicates that a clinical

drug should be effective (successful treatment), as well as cost-effective (at least in comparison to the currently used drug). The critical question facing decision-makers is: how does one make a choice among a range of alternatives? Artemisinin-based combination antimalarials have been shown to be effective by reducing clinical and parasitological treatment failure rates [46, 47] and reducing gametocyte carriage [20, 48]. To make an informed decision, policy makers, especially in resource-constrained countries, need information showing the effectiveness, costs and cost-effectiveness of a range of alternatives. However, the use of traditional economic evaluation approaches becomes inadequate in situations where the measurement of the impact of an intervention is methodologically complex. This is particularly true for the evaluation of interventions aimed at containing the public health impact of drug resistance and limiting malaria transmission [49], such as *artemisinin-based combination therapies*.

The economic evaluation of ACTs is relatively convoluted. Firstly, the nature and scope of resistance to artemisinin drugs is still unknown, and as such it is unclear how the emergence and spread of resistance to artemisinin combinations will evolve. This means that the Useful Therapeutic Life (UTL) (i.e. the length of time for which a drug continues to offer effective treatment) of ACTs is unknown. Secondly, the expected 'impact' of the widespread use of ACTs is multifaceted. In addition to improving cure rates (and the associated benefits), the impact of ACTs on transmission is expected to result in reduced malaria cases and other positive externalities resulting from that, such as lower productivity losses on the part of households and lower caseloads at health facilities. Moreover, the use of artemisinin drugs in combination with relatively cheap antimalarials (such as SP) is expected to "prolong" the UTL of each of the components of the combination, hence providing countries with opportunities to use antimalarial drugs for longer. Thirdly, there are several factors (such us compliance of patients in taking drugs and proportion of population using ACTs) that influence the effectiveness of ACTs which pose difficulties in the measurement of the 'impact' of ACTs. The issue of *compliance* becomes particularly critical if the combination drugs are not co-formulated, and also in countries where there is both inadequate pharmaceuticals regulation

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failure rate of 15% and parasitological rate of 25% should not be exceeded.

and high levels of self-medication. Lastly, the benefits of ACTs only occur in patients infected with malaria, motivating for limiting their use to those with a definitive (rather than clinical) diagnosis of malaria, provided this approach is cost-effective.

More specific to this study, the evaluation of artemether-lumefantrine (AL) in the Kwazulu Natal setting is fraught with difficulties of disaggregating the impact of AL from the total impact of the other malaria control interventions that were implemented in rapid succession in this study site. At the time of change of treatment policy in Kwazulu Natal, two other important malaria control interventions were also implemented which made it difficult to attribute the observed changes in malaria prevalence to any one of them. In light of this, this study focuses on the evaluation of ACTs within the context of effective vector control and routine use of definitive diagnosis as the basis for the provision of antimalarial treatment.

1.3: STUDY AIM AND OBJECTIVES

This study seeks to use the techniques of cost-effectiveness analysis to evaluate, within the context of effective vector control, the change to ACTs as first line malaria treatment and to evaluate the relevance of using definitive diagnosis (as opposed to clinical diagnosis) as the basis for initiating malaria treatment, especially when using ACTs for treatment. Kwazulu Natal switched from SP monotherapy to AL in 2001 while Mpumalanga changed from SP to AS+SP in 2003. The use of rapid diagnostic tests (RDTs) and subsequently ACTs (AS+SP) were implemented at pilot level in Namaacha and Matutuine districts (southern Mozambique) in 2003. Since the policy decision to change to ACTs had already been made in Kwazulu Natal and Mpumalanga, cost-effectiveness studies for these two ACTs were mainly for purposes of evaluating the policy decisions and for generating information that could inform international policy and provide evidence that could be used by other countries. In the case of Mozambique, the economic evaluation results of using RDTs together with ACTs would provide information for decision-making on matters relating to the wide-scale implementation of routine use of RDTs in the rest of the country. The results of cost-effectiveness of ACTs in Mozambique do not form part of this thesis.

More specifically, the objectives of this study are to:

1. quantify the impact, in terms of health outcomes, associated with the use of ACTs as first line treatment in Kwazulu Natal and Mpumalanga;
2. define and calculate cost savings (or additional costs) resulting from the change of treatment policy from monotherapy to ACTs in Kwazulu Natal and Mpumalanga;
3. compare the cost-effectiveness of two ACTs (AL and AS+SP) relative to SP;
4. calculate the costs associated with the use of Rapid Diagnostic Tests (RDTs) to explore the role of introducing definitive diagnosis together with the change to ACTs using data from the two pilot districts in Mozambique;
5. explore the use of economic models and Delphi surveys as a way of dealing with methodological challenges in economic evaluations; and to
6. provide recommendations on the cost-effectiveness of ACTs and RDTs, in southern African settings with effective vector control programmes.

1.4: CONCLUSION

The development and spread of resistance to antimalarial drugs is a global threat. With malaria being one of the three major killers and having a very high burden of disease in the world, it is essential that effective control and management of malaria cases be given absolute priority. Prompt, effective treatment is considered to be one of the most fundamental strategies of containing the disease and its impact. This means that antimalarials used for first line treatment need to be very effective, affordable, available and accessible. This is particularly crucial for sub-Saharan African countries that are already struggling with the highest malaria burden, as well as high levels of poverty, limited health care resources and other disease burdens.

Increasing and rapid spread of resistance to traditional (and cheap) antimalarials calls for decisions to be made about the adoption of more effective antimalarials, particularly in countries with high malaria disease burdens. To date, ACTs are promising not only to offer rapid and effective treatment of uncomplicated malaria, but also to delay the emergence of

resistance to antimalarials and to reduce malaria transmission. There are a limited number of antimalarials currently available and even fewer ACTs on the market today. The decision to make a choice among a limited range of options of antimalarials should be guided by evidence on the economic evaluation of the antimalarials being considered. Considering the relatively high prices of ACTs and the need to ensure that resistance to these drugs does not develop quickly, it is imperative to promote and ensure more rational use of these drugs. In addition to improving regulation of antimalarial supplies and regulations on prescribing practices in the private and informal sectors, one way of promoting rational use of antimalarials is to provide them to only those who need them by first confirming, through definitive diagnosis, that malaria is the cause of illness in febrile cases.

This study seeks to undertake the economic evaluation of ACTs in Kwazulu Natal and Mpumalanga provinces (South Africa) within the context of effective vector control, using the cost-effectiveness approach, and to evaluate the role of using definitive malaria diagnosis before treatment as a way of promoting rational use of drugs and enhancing their cost-effectiveness.

The rest of this thesis is structured as follows: an analytic review of the literature and conceptual framework are presented in chapter 2; and the general methods in the cost-effectiveness analyses of ACTs and evaluation of malaria rapid diagnostic tests are discussed in chapter 3. Methods used in a specific study site (to take into consideration the differences in contextual issues) as well as the findings on the cost-effectiveness analyses in the different study sites are presented in chapters 4-6. Chapter 4 covers the cost-effectiveness analysis of ACTs in Kwazulu Natal; chapter 5 provides a comparison of the cost-effectiveness analysis of ACTs in Kwazulu Natal and Mpumalanga; and chapter 6 explores the cost-effectiveness of RDTs in southern Mozambique. Chapter 7 presents an overall discussion of the important findings on cost-effectiveness of ACTs and RDTs in the southern Africa context and the broader relevance of these findings to other settings. Lastly, chapter 8 draws on the key conclusions and recommendations made on the basis of the findings from all study sites and provides suggestions on areas for future research.

2. LITERATURE REVIEW

2.0: INTRODUCTION

This chapter provides a critical review of the literature on malaria, malaria diagnosis, management and control, drug resistance to antimalarials, economic evaluation techniques and economic modelling. It highlights crucial issues, experiences, methods and lessons learned from previous research about the above subjects.

This chapter is structured as follows: a general background on malaria, its burden, control and management is presented in section 2.1; this is followed by a discussion on the phenomenon of drug resistance in general and the growth of resistance to antimalarials in particular in section 2.2. Section 2.3 provides a summary of the literature on malaria diagnosis. Section 2.4 provides basic definitions of the different economic evaluation approaches and their limitations, while in section 2.5 a detailed exposition of the techniques used in cost-effectiveness analysis is presented. In section 2.6, the role of modelling in economic evaluations is explored. Section 2.7 provides a brief summary of the literature review on the economic evaluation of malaria control interventions. Section 2.8 describes the conceptual framework of the study. Lastly, a summary of points salient to this thesis arising from the literature review as a whole is presented in section 2.9.

2.1: MALARIA

2.1.1: Introduction

The term ***malaria*** refers to the disease caused by the infection with any of the four human parasites of the genus *Plasmodium* (*P. Falciparum, P. Vivax, P. Ovale and P. Malariae*). This thesis focuses on *Plasmodium falciparum*, being the most dangerous of the four parasites and accounting for the majority of malaria cases in Africa [2, 10]. A female *Anopheles*

mosquito transmits these parasites from person to person. The *Anopheles gambie* complex is the commonest species member throughout sub-Saharan Africa (SSA), the most effective malaria vector and the most difficult to control [16, 50]. Malaria parasites can also be transmitted from person to person by the inoculation of infected blood, whether intentionally or accidentally, through blood transfusion or sharing of injection needles [51].

Uncomplicated malaria usually presents as a febrile illness associated with various symptoms including headaches, fever, general weakness, stomach pains, and painful joints. Severe malaria manifestations include cerebral malaria, severe anaemia, and kidney and other organ dysfunction. Diagnosis of malaria based on signs and symptoms (clinical diagnosis) is often inaccurate because these symptoms overlap with those of several febrile infectious diseases [2, 3, 7]. As such, methods (such as household surveys) that require respondents to answer questions about previous 'malaria episodes' are challenged with the fact that respondents might refer to 'fever episodes' that might or might not be true malaria episodes.[2] Other studies that have used household surveys to study the impact of malaria have also faced this challenge and have relied on asking respondents about previous malaria episodes based on symptoms rather than parasitological diagnosis of the disease [52-56]. Definitive diagnosis of malaria can be done using microscopy through testing of blood smears or rapid diagnostic tests [2, 3, 6, 7, 11, 57-62]. However, due to lack of proper testing facilities in most malaria endemic countries, diagnosis in malaria endemic areas is most often clinically based. Uncomplicated malaria, if diagnosed early, can be relatively easily treated [63]. An episode of uncomplicated malaria, when treated with an effective drug, lasts a few days.

In areas with high intensity transmission of malaria, repeated exposure to the disease sometimes results in the development of protective immunity. The population that does not develop this immunity remains at risk of progressing to severe malaria [16, 64]. Malaria is

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[2] It is important to note that for the household survey reported later in this thesis, it is highly unlikely that the 'malaria episodes' referred to by the respondents were not true malaria cases. This is because almost all malaria cases in the study areas are definitively diagnosed at a health facility before treatment. Moreover, it was established through the household survey that nearly all malaria cases (98%) are treated at formal health facilities. However, some true cases of malaria that were considered by the household head to be "other (non-malaria) febrile" illnesses would have been excluded from the evaluation of the household costs of malaria treatment.

most dangerous in children and is a cause of chronic anaemia, as well as contributing to other childhood diseases [27, 50]. Because young children lack natural immunity, they are more likely to develop severe malaria (e.g. cerebral malaria or severe anaemia), and are at increased risk of malaria-related death. Malaria is reported to kill 10-50% of children with severe malaria, even with treatment [64]. Malaria also poses a particular danger to pregnant women, as malaria in pregnancy is associated with usually resulting low birth weight, premature delivery, abortion, hypoglycaemia, severe anaemia, and maternal death [27, 50, 63]. It is estimated that 400,000 pregnant women in Africa develop severe anaemia from malaria, resulting in 10,000 maternal deaths every year [64].

Cerebral malaria (caused by *P. falciparum* infections) and severe malaria are the most common malaria complications and causes of death. In some areas, cerebral malaria could represent as much as 50% of all cases of *falciparum* malaria admitted to hospital and 80% of fatal malaria cases. Most malaria mortality occurs exclusively in *P. falciparum* infections, and even if the disease may have a rapid fatal course in children, mortality rapidly declines when effective treatment becomes widely available and used.

Patterns of malaria transmission are categorised as either being stable (endemic) or unstable (epidemic) [27, 65]. Goodman and others describe 'stable transmission' as "*transmission from year-to-year, albeit with the possibility of wide seasonal variation in transmission intensity and disease incidence*" [27, p.2]. Malaria transmission in sub-Saharan Africa (SSA) is generally classified as stable, with intense, perennial transmission of *Plasmodium falciparum*, although areas in southern Africa have unstable, low intensity, seasonal malaria transmission. There is a need for further knowledge about the complexities surrounding the disease, its transmission, and the implications of a reservoir of people with asymptomatic parasitaemia [16]. Given the complexity and the lack of full knowledge of the relationship between transmission intensity, control strategies and health outcomes, Goodman and others note the importance of the use of models as analytic and predictive tools for assessing malaria burden, designing appropriate malaria control strategies and predicting the effectiveness of malaria strategies [27].

2.1.2: Burden of disease

Malaria is the world's leading parasitic infection and the is one of the leading causes of morbidity and mortality in the tropics [2, 3, 10, 50, 66]. Since 1998, the World Health Organisation has identified malaria as a key priority, as evidenced by the establishment of the Roll Back Malaria (RBM) campaign. To date various interest groups have established global initiatives and partnerships with the aim to undertake malaria-related activities and research. Such initiatives include the Multilateral Initiative on Malaria (MIM), the Medicines for Malaria Venture (MMV) and the Global Fund to fight AIDS, TB and Malaria.

Malaria has been, and continues to be, a central focus of attention for health authorities in most of the endemic countries since the earliest stages of development of disease-specific morbidity and mortality statistics. However, the compilation of accurate statistics on malaria and the true scale of the burden is still hampered by arduous challenges including the dynamic nature of the disease [3], the large scale of the disease problem, the weak health information systems, the fact that most malaria cases, treatment and deaths occur outside the formal health sectors [50], and the extensive dependence on clinical diagnosis (even when patients are seen in the formal health care sector) which make it difficult to have precise malaria data. Moreover, inter-country comparability remains a problematic area especially due to the lack of standardisation of definitions and procedures by the malaria control programs in different countries. While official statistics provide the best global estimate of *incidence of malaria*, reliable data on *mortality* has been more difficult to obtain, especially because malaria deaths occur outside the formal health sector and also because malaria symptoms are non-specific [2, 51]. Estimates by the World Health Organisation indicate that there are 350–500 million clinical cases of malaria each year [3]. These figures may be a significant under-estimate of the true malaria toll considering that the greatest impact of malaria occurs in areas where surveillance systems are weak [2, 66]. On the other hand, however, it is possible that these statistics are grossly over-estimated given that the areas where the greatest proportion of malaria cases occur rely on clinical diagnosis of malaria which can be an overestimate, as these often include many other acute febrile illnesses.

Malaria is considered to be endemic in 107 countries, and the prevalence of malaria has been alarmingly increasing, particularly in Africa [16, 50]. In sub-Saharan Africa, the world's most affected region, malaria-related illnesses are estimated to claim the lives of 1 million children every year. Moreover, up to 90% of the estimated 350-500 million new clinical malaria cases per year occur in sub-Saharan Africa [3, 27, 50]. Meanwhile, most malaria illnesses are not treated in the formal health facilities (so are not likely to be captured by these information systems), hence these global estimates are extrapolated from research reports for both morbidity and mortality. The risk of malaria-related morbidity and death is highest for young children, pregnant women as well as travellers from non-endemic countries [10]. Severe malaria is also noted to be increasing in older children and young adults [16, 51]. It is suggested that this increase in severe malaria in older children may be a result of growing urbanisation and use of antimalarials and personal protection, which reduce infection risk but delay the development of immunity [51]. An increasing incidence of imported cases of malaria, especially in industrialised malaria-free countries has been noted [16].

The gigantic burden of malaria to an individual, a household and the entire country – in the short- and long-term – results in health, social and economic costs. In addition to prevention and treatment costs, malaria is associated with over-burdened health systems, treatment seeking costs, lost productivity, retarded physical and cognitive development in children, other neurological sequelae, and retarded economic growth through reduced tourism and business investment and an incapacitated labour force [2]. Sachs and Malaney estimated that malaria causes a 1.3% reduction in annual per capita economic growth rate of malaria endemic countries [9]. The biggest burden of this disease is particularly felt by the poor and the vulnerable [3, 7], usually residing in the rural areas with poor access to health services. The World Health Organisation reports that "*both direct and indirect costs of health can be a substantial burden to poor households which may spend up to 34% of their total income on health care*" [3, p.12].

2.1.3: Malaria Control

Malaria control efforts world-wide are focused on several approaches including: vector control (i.e. targeting the control of the mosquitoes that transmit malaria through widespread use of indoor residual insecticide spraying (IRS) and insecticide treated bed nets (ITNs)), minimising the number of infective bites (especially through bed net use), ensuring early diagnosis and effective treatment, and preventing malaria in high risk groups through intermittent presumptive / preventive treatment or chemoprophylaxis [2, 3, 8, 10, 11, 67-72]. In view of the complexities of malaria vaccine development, and the fact that global eradication of the anopheles mosquito is not feasible (especially given the gradual development of resistance to insecticides), policy makers are now concerned with strategies that focus on improving medical treatment for infected people. Integrated approaches including vector control, use of insecticide-treated bed nets and effective treatment have been recommended [73]. However, their successful implementation has been severely hampered by various obstacles, including, constrained budgetary resources, the emergence and spread of resistance to antimalarials and residual insecticides, lack of adequate health services infrastructure, cultural beliefs and practices, and poor coordination and collaboration amongst malaria control initiatives [11, 16, 27].

2.1.4: Malaria and its control in Southern Africa

Southern Africa is made up of eleven countries, including Angola, Botswana, Lesotho, Malawi, Mozambique, Namibia, Tanzania, South Africa, Swaziland, Zambia and Zimbabwe. *Plasmodium falciparum* (spread by *Anopheles Arabiensis, Anopheles Gambiae* and *Anophelese funestus*) is responsible for the majority of malaria infections in Southern Africa. Out of an estimated total population of 140 million people who live in the region, about 88.5 million (63%) of these are living in malarious areas. Of the people living in malarious areas 15.6 million (17.6%) are children (< 5 years) and 3.7 million (4.2%) are pregnant women [65]. Within the region, some areas are malaria-free (Lesotho and parts of South Africa, Botswana and Namibia), some areas have unstable malaria transmission (border areas of South Africa, Namibia, Botswana, and some small parts of Zimbabwe and Tanzania), while the rest has stable malaria transmission [65].

Malaria is reported as the major cause of morbidity and mortality in Southern Africa, with a case fatality rate of 0.2-2.4% and 1.8-9.6% in South Africa and Mozambique, respectively [65]. Malaria also accounts for 24% of outpatient attendances and 50% of inpatient deaths in Mozambique (*ibid.*). Key malaria-related and other indicators for Mozambique and South Africa are presented in Table 2 1 below.

Table 2.1: Malaria transmission & burden in Mozambique and South Africa

Indicator	Mozambique	South Africa
Human development index (rank and score)	168/174 (0.341)	103/174 (0.697)
Total population (1998)	16,118,000	44,296,00
Health expenditure as % of total public expenditure (1997)	9.3	9.8
% of population living in malarious areas	100%	10%
Type of transmission	Stable and unstable	Malaria-free & unstable
Main malaria vectors	Gambiae, funestus	Arabiensis
Predominant Parasite species	P. Falciparum	P. Falciparum
Population at risk of malaria	16,118,000	4,429,500
Reported number of malaria deaths per annum (1995-99) Estimated number of malaria deaths per annum	450 – 941 44,250 – 67,000	12 – 402 450 – 690
Reported malaria incidence/1000 population per annum (1995-99) Reported malaria incidence/1000 population at risk per annum	12 – 84 121	0.2 – 1.1 6.7
Estimated malaria prevalence (2 – 9 years)	40 – 60%	0 – 5%

Source: *Adapted from Southern Africa Malaria Control Review (pp. 71 – 73).*

The initiative to reduce malaria transmission, morbidity and mortality has resulted in extensive multilateral efforts focused on malaria control and management in Southern Africa. The overall regional effort to "roll back malaria" includes strategies such as integrating malaria control as part of public health systems, human resource capacity building, surveillance and early detection of epidemics, vector control, improved drug supply and management, improved case management, health promotion and education, promotion of use of insecticide-treated bed nets, as well as drugs and insecticide resistance monitoring [65]. This regional effort has been facilitated by the political commitment of all governments involved as well as the South African Development Community (SADC). Each of the strategies listed above has been constrained by various factors. Constraints that are of critical relevance to

this study include: [65]

- ★ Difficulty for individuals and institutions to come together on a common platform of malaria service delivery and malaria control;
- ★ Non-standardised surveillance data across the region with some countries having poor coverage;
- ★ Lack of human resource capacity with specialist training in malaria control and surveillance;
- ★ Weak reporting and information systems; and
- ★ The development and rapid spread of resistance to antimalarials and insecticides.

Given the variations in antimalarial resistance, intensity of transmission and other socio-economic factors, first line treatment policies in the Southern African countries differ. In Mozambique, chloroquine was used as the first line drug for uncomplicated malaria and SP is used for second line treatment, except during epidemics when SP is used as the first line drug. In South Africa, until 2001 SP was used as first line treatment in all the malarious provinces. Given the high levels of resistance to both chloroquine and SP, both Mozambique and South Africa considered the replacement of the traditional monotherapy drugs with more effective ones, particularly ACTs. To date, all three malarious provinces in South Africa have successfully replaced SP monotherapy with either Coartem®, a fixed combination of lumefatrine and artemether (Kwazulu Natal and Limpopo provinces) or with a combination of artesunate *plus* SP (in Mpumalanga province). Mozambique is carefully considering a change to an artemisinin-based combination, possibly artesunate *plus* SP, which has been implemented and studied at pilot level in two districts in southern Mozambique.

The change of first line malaria treatment becomes necessary when the levels of resistance to a drug are high, resulting in 'unacceptable' levels of treatment failure. As this was the case in Kwazulu Natal in 2000, the need to change to more effective antimalarials became inevitable. In order to assess the potential impact of such a change in treatment policy, it is important to understand the complex field of drug resistance development. A brief exposition of the drug resistance phenomenon follows.

2.2: ANTIMALARIAL DRUG RESISTANCE

Currently there are several antimalarials on the market including: chloroquine, amodiaquine, mefloquine, sulphadoxine-pyrimethamine, quinine and artemisinin and its derivatives. Although an uncomplicated malaria episode can be cured with a relatively short course of an effective antimalarial, major challenges remain because of the existence of selection pressures, coupled with incomplete treatment (through under-dosing, sub-standard antimalarials and or poor compliance). The challenges have resulted in the development and spread of resistance to the commonly used antimalarials [16, 27, 74, 75]. Chloroquine resistance is already widespread with high levels of treatment failure [14]. Although SP was introduced as first line treatment much later than CQ in Africa, resistance to SP and treatment failure associated with its use are already prevalent and are expected to increase rapidly [20, 21]. Such findings make it essential for governments and international institutions, engaged in the fight against malaria, to find cost-effective strategies that not only delay the emergence of resistance but also continue to provide effective treatment.

2.2.1: Antimicrobial Resistance in General

Following the wonderful discoveries of antimicrobials and the development of new technologies that have tremendously changed ways of managing and treating infectious diseases, we now face the challenge of drug resistance. The discovery of antimicrobials was much celebrated because their use resulted in a complete transformation in the understanding and treatment of infectious diseases [19]. Unfortunately, however, these drugs are now becoming increasingly threatened by the emergence of 'resistance'. In a WHO Report on Infectious diseases, the Director-General highlights that "... *at the dawn of the new millennium, humanity is faced with another crisis. Formerly curable diseases such as gonorrhoea and typhoid are rapidly becoming difficult to treat, while old killers such as tuberculosis and malaria are now arrayed in the increasingly impenetrable armour of antimicrobial resistance*" [76, p.1].

Infectious diseases are caused by microbes (bacteria, fungi, parasites and viruses). The use of antimicrobial agents to treat infections over a period of time forces microbes to die or adapt [18]. The development of resistance is a natural biological phenomenon, where microbes develop resistance through a process known as *natural selection*. When a population of microbes is exposed to a drug, the *susceptible* microbes die, while those carrying resistant genes adapt to the drug. These resistant organisms "can then pass on their genes to their offspring by replication, or to other related bacteria through 'conjugation' whereby plasmids carrying the genes 'jump' from one organism to another. This process is a natural unstoppable phenomenon..." [19, p.9]. These resistant microbes continue to be transmitted to humans in normal ways, causing infections that are completely resistant to the antimicrobial in question. This means that an infection with resistant microbes can only be treated with another antimicrobial to which these microbes have not developed resistance.

The overuse and misuse of antimicrobial agents in human and veterinary medicine, agriculture and aquaculture are believed to play a major role in the emergence and spread of resistance [17-19]. Other factors that influence the development and spread of resistance include: poverty and inadequate access to quality drugs; misdiagnosis and self-medication; availability of counterfeit or poor-quality drugs; international travel; poor prescribing practises and poor compliance with antimicrobials [19].

Since the first case of resistance to *Staphlylococcus aureus*, the problem of drug resistance has rapidly emerged to many drugs such as those used in the treatment of tuberculosis, cholera, malaria and pneumonia, to mention but a few [76]. Concerns around the drug resistance problem are very legitimate when one considers the social, economic and political implications of the problem, both at national and global levels. Generally speaking, if not contained, drug resistance has the potential to have a devastating impact, as documented by some authors [19, 27, 77, 78], including:

- ★ High levels of disease burden, in terms of both morbidity and mortality;
- ★ Direct costs associated with re-treating people who fail treatment with certain drugs, as well as the need to use more expensive drugs and in some cases to

hospitalise patients who deteriorate to severe forms of diseases;

- ★ Direct household costs (associated with treatment seeking) and indirect costs associated with increased morbidity, which include reduced labour productivity and its negative effect on economic growth, impact on land use, and impact on children's school attendance and cognitive skills; and,
- ★ Costs associated with loss of the drug as a resource, and the need to replace it with a more effective drug, as well as the need for research and development of new drugs.

2.2.2: Resistance to Antimalarials

Drug resistance of malaria parasites has been defined as " ... *the ability of a parasite to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the subject*" [63, p.8]. In other words, resistant parasites are those that are not killed by an antimalarial after a standard course of treatment.

The phenomenon of drug resistance in *P. falciparum* has been known since 1910 when some infections with this species in Brazil failed to respond to quinine administered in a dose regimen that would normally have produced a cure [79]. Resistance to Chloroquine was first discovered in South East Asia and South America in the late 1950s and is now widespread in at least 80% of the 92 countries where malaria continues to be a major killer [19]. Resistance to other drugs (e.g. amodiaquine and SP) follows a similar pattern and is becoming widespread, while resistance to drugs such mefloquine has started developing in SE Asia [19, 74, 79]. In Southern Africa, resistance to chloroquine is already widespread, and there are very high levels of resistance to SP in certain parts (e.g. Kwazulu-Natal, South Africa).

Resistance to antimalarials arises as a result of spontaneously occurring mutations of parasites that select for a drug [63]. The dynamics of the evolution and spread of drug-resistant malaria are complex and not fully known [80]. During the last few decades,

resistance to antimalarials has become a critical problem as these drugs are being used more frequently for prophylaxis and self-medication, often in insufficient doses, and more widely used for treatment (whether controlled or uncontrolled). Antimalarial resistance is a problem because infections caused by resistant parasites result in treatment failure with most commonly used first line antimalarials. Typically, consequences of resistance have serious cost implications and result in the overburdening of weak health care systems, especially for highly endemic and yet poor sub-Saharan African countries. Most of these implications are in the form of higher costs resulting from increases in morbidity rates, prolonged illness and hospitalisation, additional laboratory tests, as well as the use of more expensive second- and third-line drugs. Furthermore, there are costs accrued by the patients and/or their households, in the form of treatment seeking (travel costs) and lost income due to time away from work.

Resistance to antimalarials raises a two-fold global concern. Firstly, until recently when a few antimalarials started being developed, the pace at which resistance was developing to the traditional monotherapy antimalarials was much faster than the pace at which new antimalarial drugs were being developed [19] and secondly, newly developed antimalarials become successively more expensive than the ones presently available on the market [15], hence becoming 'unaffordable' for the countries that need them the most. These two concerns underscore the need to find strategies that delay the emergence and reduce transmission of resistance to affordable antimalarials. Given the inevitability of the emergence of drug resistance, finding cost-effective strategies that mitigate the impact of resistance becomes of paramount importance.

Recently, the use of combination antimalarial therapies was identified as a key strategy with the potential to contain the emergence and spread of resistance to antimalarials. Combination antimalarial therapy is defined as "*the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and different biochemical targets in the parasite*" [75, p.7]. Considering the synergistic potential of two or more drugs, combination therapies are believed to improve therapeutic efficacy and also to delay the development of resistance of the individual drug components of the combination. Types of possible combinations include

the **non-Artemisinin based combinations**[3] (e.g. CQ+SP; AQ+SP; MQ+SP; Atovaquone-proguanil) as well as the **Artemisinin based combinations** (e.g. CQ+AS; AQ+AS; SP+AS; MQ+AS; Artemether-Lumefatrine). Each of these combinations has its strengths and weaknesses in terms of efficacy, side effects, potential use in pregnancy and their pharmacodynamic and pharmacokinetic properties. Similarly, all combination therapies in general have factors in their favour and potential prohibitive factors [75]. A WHO publication outlines the challenges to be considered in the implementation and use of combination antimalarial therapies in Africa as: [75, p.8]

- ★ The choice of drug combinations best suited for the different epidemiological situations
- ★ The cost of combination therapy
- ★ The timing of the introduction of combination therapies (e.g. should they be implemented in areas where monotherapy is still effective?)
- ★ The operational obstacles to implementation, especially compliance.

The strategy of using artemisinin-based combination antimalarials for the treatment of uncomplicated malaria has recently become strongly recommended. Artemisinin-based combination therapy (ACT) is an antimalarial combination with an artemisinin derivative as one component of the combination [75]. Unlike other antimalarials, artemisinins have been shown to directly reduce malaria transmission by decreasing gametocytes. In addition to rapid and effective treatment of malaria, artemisinin-based combination therapy (ACT) has been shown to improve cure rates, decrease malaria transmission and delay antimalarial resistance on the northwest border of Thailand [81]. Improved cure rates and decreased gametocyte carriage have been confirmed in clinical trials of ACTs in Africa [24, 81]. Furthermore, these combination antimalarial therapies have been found to be cost effective in some contexts [26].

There is growing international consensus that wide-scale, systematic implementation of ACT is one of few effective measures that will enable malaria endemic countries to achieve the

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[3] Drug abbreviations stand for: CQ = Chloroquine; SP = Sulfadoxine-Pyremethamine; AQ = Amodiaquine; MQ = Mefloquine; AS = Artesunate.

ambitious goals set in Abuja in 2000 to "Roll Back Malaria", particularly that of halving malaria morbidity and mortality by 2010. The World Health Organisation (WHO) explicitly recommended "*the use of Artemisinin based combination therapy" in order to "provide effective treatment against malaria and to slow the spread of drug resistance*" in a statement released on 20 February 2001. Despite their ability to improve malaria health outcomes, the cost and affordability of ACTs continue to be a key area for policy debate for countries considering their use, particularly those in Sub-Saharan Africa. This trade off between achieving improved health outcomes through a more effective drug and having to buy antimalarials at a relatively higher price requires careful evaluation to ascertain whether the additional resources spent are 'buying' a 'reasonable' amount of health outcomes.

2.3: MALARIA DIAGNOSIS

Early diagnosis and prompt effective treatment form fundamental components of WHO's global strategy for malaria [63]. However, the diagnosis of malaria remains a problematic issue, especially in African countries lacking appropriate diagnostic facilities. This problem has resulted in clinical diagnoses based purely on the symptoms that a person presents with. Unfortunately, the symptoms for malaria (especially fever) are common to many other diseases; hence symptoms-based diagnoses are likely to be inaccurate [27]. As a result, antimalarials are prescribed to patients who do not have malaria while some patients with malaria parasites are left untreated. The lack of appropriate diagnostic tools at health facilities, confounded by inaccessibility to health services, has resulted in high levels of self medication and incorrect use of antimalarials, particularly in Africa. Such misuse of antimalarials, under-dosing, poor adherence and sub-standard drugs are partly responsible for the rapid emergence and spread of resistance to these drugs.

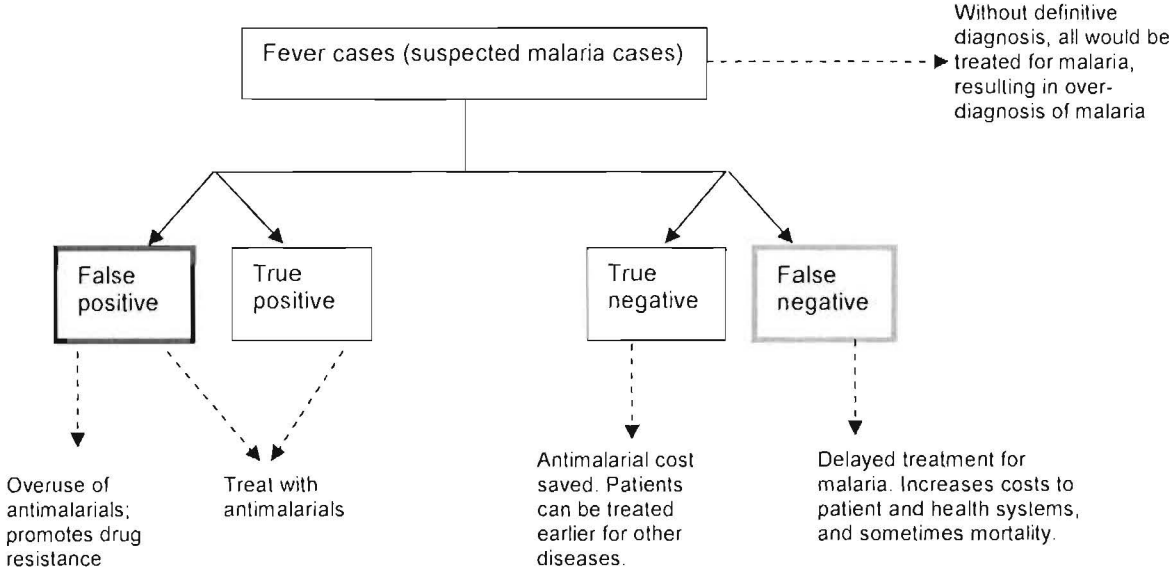
Microscopic examination (of both thin and thick blood films) is the accepted laboratory practice for the diagnosis of malaria [57, 60, 82]. One of the key advantages of microscopy is its high sensitivity and specificity. Microscopy sensitivity (with experienced microscopists) with

the thick blood film is 50 parasites/μl. However, most routine diagnosis laboratories generally achieve a lower sensitivity of detection (≅ 500 parasites/μl) [57]. Other advantages include its ability to identify the infecting parasite species and to quantify parasite density (which is valuable as uncomplicated hyperparasitaemia is associated with increased malaria mortality), and the potential use of the same technique for the diagnosis of other diseases [60]. On the other hand, the microscopy technique is time-, labour- and equipment-intensive and requires skilled personnel as well as regular quality assurance and supervision. There has been little improvement of the blood film technique since the early 1990s. With the microscopy approach, staining can take up to 60 minutes of preparation and is labour-intensive [57]. The urgency to get malaria test results quickly before initiating treatment renders such a diagnostic approach impractical for routine testing. Also, a *Plasmodium falciparum* infection may be easily missed when there is insufficient number of parasites for detection in the blood films (where parasites may be sequestered in the deep capillaries) [57, 60, 83]. Although there is a logistical burden associated with performing a time-, labour- and equipment-intensive procedure (e.g. microscopy), it is the training required to establish and sustain competent performance of microscopy that poses the greatest difficulty in employing this diagnostic technology, especially in rural areas [82]. Economic evaluation studies comparing microscopy with clinical/presumptive diagnosis demonstrate that microscopy is more cost-effective and sometimes even cost-saving. For example, Jonkman and others (1995) found that treating adult malaria outpatients in Malawi on the basis of a microscopy test cost less than treating them on the basis of clinical diagnosis [84].

Non-microscopic rapid diagnostic tests (RDTs) are lateral flow immunochromatographic devices, which detect specific antigens (usually histidine-rich protein-2 or a parasite specific lactate dehydrogenase) that are present in the blood of infected or recently infected people [57]. As microscopy is difficult to maintain in remote and poorly resourced areas, rapid diagnostic tests (RDTs) offer the potential to provide accurate diagnosis to those unable to access good quality microscopy services [2, 7, 57, 58, 60, 61, 83, 85, 86]. Rapid diagnosis for malaria should be accurate, sensitive and cost-effective. According to the WHO recommendations [83], RDTs should be at least as accurate as the results derived from

microscopy performed by an average technician under routine field conditions. Sensitivity of RDTs should be above 95% compared to microscopy and the RDT should be capable of detecting parasitaemia at 100 parasites/μl from all *Plasmodium* species.

Despite offering the possibility of more rapid and more practical methods for malaria diagnosis in areas where microscopy approaches are not feasible, sensitivity for RDTs remains a problem, particularly for non-immune populations [57]. The illustration below demonstrates the problems associated with low sensitivity and specificity of RDTs.



Sensitivity of a RDT refers to its ability to accurately detect all the true positives and to minimise the number of false negatives. The higher the number of false negatives the lower the sensitivity of the RDT. On the other hand, *specificity* refers to its ability to correctly diagnose the true negatives and to minimise the number of false positives. RDTs with a high false positive rate have a low specificity. The higher the sensitivity and specificity of a RDT the better it is at offering accurate diagnosis for malaria.

Extensive field trials of some RDTs (such as ParaSight F, ICT PF, and PATH Falciparum) have been undertaken [6, 57, 82, 85, 87-92] and varying results on the performance of these RDTs are reported. For example, a sensitivity of 77% - 98% and specificity of 83% - 98%, using thick blood film microscopy as the comparative standard (for > 100 parasites/μl) have been reported for ParaSight F [57, 82, 91, 92]. When compared with PCR results, Humar and others and Pieroni and others reported a sensitivity of 88% and specificity of 97% for ParaSight F [91, 92]. In a comparative study undertaken in 2 countries (Thailand and Peru), Forney and others found that the sensitivity for the ParaSight F test were different in the different settings and were unable to explain the difference in performance in the different study sites, despite the considerable rigor exerted in standardising the protocol execution between the study sites [82]. Mills and others report sensitivity and specificity of 96% and 99% respectively for PATH Pf based on a study among 148 oversees travellers [88]. OptiMAL, when compared to microscopy, has been reported to have an overall sensitivity for Plasmodium falciparum and Vivax of 94% and 88% respectively, and specificity of 100% and 99% respectively, in a study involving 202 patients in Honduras. In another field study, Quitana and others report a sensitivity and specificity of 100% and 95% respectively for OptiMAL, although when compared to the PCR results the OptiMAL test was unable to detect mixed infections [90]. The ICT test (studied among 153 travellers in the United Kingdom – doing self testing), was found to have sensitivity of 95% and specificity of 97% when compared with expert microscopy [57]. In another study of ICT in Thailand, a strong positive test was reported to be highly predictive of Plasmodium falciparum asexual parasitaemia for the diagnosis of new cases, but a negative result was reported to be inadequate to exclude parasitaemia of < 300 parasites/μl [57].

A key limitation of the RDTs is that a negative RDT test result does not always exclude malaria with certainty because there may be insufficient parasites to be detected by the test, the RDT may be damaged (hence reducing its sensitivity) and the infection might be caused by another species of malaria parasite which the RDT is not designed to detect [83]. Non-falciparum malaria diagnosis would be missed with the HRP-2-based tests. In areas of high intensity malaria transmission, a positive result does not always point to malaria as the cause

of illness because a high proportion of the population have asymptomatic parasitaemia. The presence of other substances in the blood (such a Rheumatoid factor) may produce a false positive result, and the antigen may be detected after the infecting parasites have died or due to the persistence of malaria gametocytes after effective treatment [57, 83]. HRP-2 has been shown to persist and is detectable after the clinical symptoms of malaria have disappeared and the parasites have apparently been cleared from the host [57].

A key issue for debate around the widespread use of RDTs, apart from their accuracy (sensitivity and specificity) in diagnosing the disease, is around their costs and affordability to poorly resourced countries. Bell correctly points out that the usefulness of RDTs in case management depends on the level of cost-savings accruing from their use [58]. Obviously, the more expensive the antimalarial used for treatment, the more likely that RDTs will be cost-saving. Based on the modelling results, Goodman and others reported an incremental cost per dipstick test of between $1.26 and $1.84 for low income countries, $1.30 and $ 1.89 for middle income countries and $ 1.69 and $ 2.31 in higher income countries [27]. They further report that savings in drugs costs resulting from the use of definitive diagnosis depends on the accuracy of clinical diagnosis, the accuracy of the test and the cost of the antimalarial used. The cost-effectiveness of RDTs is highly dependent on the prices of RDTs and antimalarials, malaria prevalence, and the effect of RDT use on treatment practices.

Other methods for malaria diagnosis include Fluorescence microscopy and Polymerase Chain Reaction [57]: Fluorescence microscopy relies on using fluorescent dyes and UV light at an appropriate wavelength to detect parasites in a blood sample. With experience, workers using methods involving fluorescence compounds are able to detect parasites rapidly and accurately. However, these methods are unable to easily differentiate among the Plasmodium species and require special training and expensive equipment and supplies – hence becoming impractical in areas where fluorescence microscopes or adequate training are not available. Polymerase Chain Reaction (PCR) is the detection of specific nucleic-acid sequences and is not suitable for the initial diagnosis of malaria. However, its advantage lies in its sensitivity, with the ability to detect 5 parasites/μl (or less) with 100% sensitivity and

specificity, and to identify parasites to the species levels. PCR-based methods are particularly useful for studies on strain variation, mutations and studies of parasite genes involved in drug resistance. However, the PCR method is an impractical standard against which to measure routine acute malaria diagnosis because of the time involved and the technical expertise and expensive equipment required.

2.4: ECONOMIC EVALUATION

2.4.1: Introduction

Traditionally, welfare economics forms the basis for economic evaluation, where the maximisation of individual or societal utility is the main objective of resource consumption and allocation [93]. This means that the allocation of limited resources is faced with the constraint of ensuring that maximum benefits are obtained from the consumption of any quantity of resources [28, 93]. Brouwer and Koopmanschap identify 2 viewpoints on the economic foundations of economic evaluations; the welfarist approach and the decision-makers' approach. They argue that "*the foundations for methodological choices within the decision-makers perspective is viewed as 'maximising health effects from a given budget*" [43, p.440]. Within the field of health care, spiralling costs of care and the development and use of new and improved health technologies have resulted in pressures to control health care spending [28, 33, 94]. This need for optimal allocation of health care resources has led to the development of formal methods to measure and value costs and the health benefits associated with them, of health care interventions [32, 95-99].

Economic analysis concerns itself with choices. Scarcity of resources and the consequent inability to produce all desired outputs necessitates that choices be made. Such choices can be made on the basis of many criteria, but methods such as "educated guesses" or "what we did last time" are not always the best considerations in a decision to commit resources to one use instead of another. Economic analysis, thus, leads to economic evaluation, defined as "*the application of analytical methods to identify, measure and value both the* ***costs*** *and*

benefits *of alternative health care interventions in order to provide evidence regarding* ***technical*** *or* ***allocative efficiency*** *and aid decision making for resource allocation*" [30, p.158]. Hence the underlying goal of economic evaluations is to identify which health interventions or programs provide maximum aggregate health benefit for a given level of resources [32, 100]. In other words, economic evaluation is "*the comparative analysis of alternative courses of action in terms of both their costs and consequences*". Economic evaluation analyses, therefore, are seen as policy-guiding tools through their provision of information on both costs and health effects of health interventions. With the welfare objective of maximising health benefits, constrained by limited resources, decision makers are expected to allocate resources to interventions that offer relatively more health benefits given their costs.

The birth of economic evaluation can be traced as far back as the 19th Century and the refinement of its techniques has benefited from the work of several scholars and economists, such as Jules Dupuit, Vilfredo Pareto, Nicholas Kaldor, John Hicks, T. C. Schelling, Burton Weisbrod, Alan Williams and many more [31]. Robinson traces the origins of cost-benefit analysis to many years ago, when it was developed by economists to assist decision-making around public sector investment planning [101]. The human capital approach, as used in cost-benefit analysis, was the first economic evaluation technique, but its limitations[4] quickly became apparent, thus leading to the development of other forms of economic evaluation such as *cost-effectiveness analysis*, *cost-utility analysis*, and the use of contingent valuation in *cost-benefit analysis* [31].

Economic evaluation approaches include; cost-minimisation, cost-utility, cost-effectiveness and cost-benefit analysis [32, 101]. Although all the approaches are faced with methodological limitations, cost-effectiveness analysis remains the most commonly used approach in the evaluation of health care and health-related technologies [93, 102]. McGuire attributes the popularity of CEA to the growing focus on evidence-based medicine and the difficulties associated with assigning monetary value to health outcomes (in the cost-benefit

[4] Human capital approach discriminates against the unemployed, the old and women.

approach) [93]. Sloan underscores the importance of conducting economic evaluations and argues that "*despite the imperfections of these methods themselves and the lack of consensus regarding which to use, one should avoid the fallacy of analytical nihilism. However imperfect, ... they are superior to the alternative, which is global subjective human judgement unaided by formal analysis.*" [28, p. 5-6].

Over the years, there has been an increasing role for economic evaluation in health care resource allocation [35, 102-104], including the evaluation of pharmaceutical products [102]. This has, for example, resulted in the establishment of institutions whose objective is to ensure the undertaking of economic evaluations and guiding policies on allocation of health care resources. Such institutions include the National Institute for Clinical Excellence (UK), the Pharmaceutical Benefits Advisory Committee (Australia), the Canadian Co-ordinating Centre for Health Technology Assessment, and the Provincial Formulary Committees (Canada) [35].

2.4.2: Economic Evaluation approaches and their limitations

All economic evaluation techniques involve the measurement of both costs and health outcomes/benefits. Essentially the procedures and techniques of measuring costs is the same in each one of the economic evaluation approaches described below. These approaches, however, differ in their techniques of measuring and valuing health outcomes. Techniques for measuring and valuing health outcomes have been a source of major debates. Despite the limitations of the different techniques, economic evaluation studies are still conducted and the choice of method for expressing health outcomes is left to the researcher/analyst. Before the different methods of measuring health are discussed let us explore the intricacies of the term 'health'.

The confusion that surrounds the definition of "health" is an important one from the point of view of measurement, since it accounts for the diversity of content and emphasis of the variety of health indicators. As Hunt points out, "*the measurement of health is inextricably linked to two associated issues: how '**health**' is defined and the purpose for which*

measurement is designed" [105, p.7]. Generally there is little agreement on the definition of health, but the World Health Organisation (1978) definition that focuses on '**physical, social and mental well-being and not just the absence of disease** or infirmity' seems to be all encompassing. Because this definition is too wide and hence not operational, measurement of health based on this definition is untenable. Hunt identifies four categories, for which there is a different method of measurement of 'ill-health' [105]. He contends that "disease" could be discerned by reference to clinical signs and symptoms or use of diagnostic technology, and that it is the task of the medical practitioner. On the other hand, he describes "illness" as involving the experience of discomfort based on the individual's perception that a change has occurred in the customary function and/or feeling. He notes that the measurement of illness must be orientated towards the patient's point of view [105]. At another level, Hunt defines "sickness" as taken to include acts of labelling and communicating distress and might involve seeking medical care, staying away from work, and staying in bed. The measurement of sickness may involve utilisation rates of medical services or the assessment of sickness rates. Lastly, "health" is a lot more difficult to define, but could be defined by reference to the absence of disease, illness and sickness. Hunt further highlights the complexities associated with the term "healthy", which sometimes implies some moral or value judgements [105]. Even more complicated are the other terms associated with health such as "well-being" and "quality of life". Indeed, not only do concepts such as 'quality of life' and 'well-being' lack a definition, but they are so closely bound to hopes, fears, values and expectations of individuals that they cannot be easily measured [105]. Despite the lack of a proper definition of health, well-being and quality of life, extensive attempts have been made to develop and refine techniques for measuring and valuing health outcomes associated with new health technologies.

An important issue relating to economic evaluations is the *viewpoint* of the analysis. That is, whether analysis is done from the viewpoint of the patient or the public/private provider of services, or even from a societal perspective. The societal perspective is most frequently recommended [33]. The different economic evaluation approaches are briefly described in turn.

Cost-Minimisation Analysis (CMA)

This approach is normally used when comparing alternatives that result in the same outcome. In other words, this method can only be employed in situations where the alternatives give identical outcomes, but differ in costs. Such an analysis, therefore, would focus on determining which of the alternatives has least costs. In most health programs (except for clinical interventions such as surgery) it is rare to find alternatives that result in identical outcomes. For this reason, the CMA is not a commonly applied technique.

Cost-Utility Analysis (CUA)

Cost-Utility analysis focuses on the quality of health outcomes resulting from health interventions/programs [32]. It is used particularly when a program affects both morbidity and mortality and thus a common unit of outcome that combines both effects is needed. In other words, it is an appropriate method when the quality of life is *the* important outcome. To be able to measure 'quality of life' depends on the measure of utility. In addition to the issue of whose preferences are obtained, one must also consider how preferences are measured. Drummond et al note that there are 3 methods of obtaining utility values namely: judgement, values from existing literature and/or values from measurements on a sample of subjects [32]. Several methods for eliciting preferences have been developed, tested and debated in the literature [106-113]. The most preferred method is that which obtains utility values from a sample of subjects. The instruments commonly used in eliciting utility values include the rating scale, the standard gamble and the time trade-off [108]. Economists prefer to use approaches based on expected utility. Several concerns have been raised around the validity and consistency of instruments used in measuring utilities [112-114], as well as around the issue of whose preferences should be obtained [32].

The process of valuing health outcomes has 6 distinct steps that need to be taken in a specific order. Gold and others outline these steps as follows [109, p.82]:

i. identifying the relevant outcomes in terms of generic health states (including death);

ii. describing the elements of health states and their possible course over time for

individuals who receive the intervention and for those who receive each alternative;

iii. combining the elements of each health state into a single number reflecting the value assigned to that health state;

iv. integrating the values assigned to the health states with the quantity of life associated with each health state;

v estimating the probabilities of each health outcome; and

vi. using the output of (iv) and (v) to compute a numerical average outcome for each of the alternatives being compared.

One of the key debates around this process lies around the techniques used for measurement of health-related quality of life (in step 3 above). While several techniques (standard gamble, time-trade off, and visual analogue scales e.g. SF-36, EuroQol, EQ-5D) have been developed, tested, compared and debated, it is important to note that their translation, adaptation and use in contexts of developing countries is still limited [115]. In their systematic and critical review of the process of translation and adaptation of generic health-related quality of life measures, Bowden and Fox-Rushby found out of the 58 papers published between 1990 and 1999, no papers were identified for West and North Africa regions [115]. Of equal importance within the debate is the question of "whose preferences should be considered?" [116].

Another key point of contention in the debate is about the final single unit in which health outcomes should be expressed. Over the years, several health outcomes units have been defined and debated including, among others *quality-adjusted life years, healthy-years equivalents, disability-adjusted life years, disability-adjusted life expectancy* [109]. Quality-adjusted life years (QALYs) seem to be the most commonly used units. The CUA approach has many similarities to Cost-effectiveness analysis, particularly with the increased use of a single unit of health outcome – the disability-adjusted life years (DALYs) – as a health outcome measure in cost-effectiveness analyses. In fact, in some cases CUA is considered to be a form of cost-effectiveness analysis. For example, when discussing the measurement of health outcomes for a cost-effectiveness analysis, the US Panel on Cost-Effectiveness refers

to combining health-related quality of life with life expectancy data to obtain a single measure that combines morbidity and mortality [109].

Cost-Effectiveness Analysis (CEA)

As CEA will be used in this study, a detailed exposition of techniques used in CEA is presented in section 2.4 below.

Cost-Benefit Analysis (CBA)

Cost-benefit analysis is one of the main forms of economic evaluation applied to public policy decisions. CBA measures both the costs and consequences of a given intervention in monetary terms. For this reason CBA is sometimes thought to be a more desirable economic evaluation approach because of ease of comparison between costs and consequences of alternative interventions. Unlike the CEA approach, the CBA method makes it explicitly clear whether an intervention is 'worth' implementing. For instance, it is clear that any intervention whose costs exceed its benefits/consequences is not worth implementing. Analysts who have used the CBA approach have generally used either (a) the willingness-to-pay approach, or (b) the human capital approach, to assign a monetary value to health benefits.

The *willingness to pay* (WTP) approach directly evaluates the social utility of a particular project as measured by the beneficiaries themselves. The WTP approach is based on individuals' valuation of their own 'lives'. In this approach people are asked, by means of questionnaires or interviews, how much they would be willing to pay to reduce the risk of death. Put differently, the WTP approach asks people how much it is worth to them to increase their survival chances [5]

The human capital approach, on the other hand, is a market-based measure, which generally assumes that the value of an individual can be equated to their (discounted) expected future

[5] Linnerooth J (1979) noted that the term '**value of human life**' is not only provocative, but that the use of the WTP approach does not actually measure human life. Instead, it measures '**value of risk reduction**'.

earnings.[6] This approach measures the value of output (at market prices) that an individual can produce in his or her lifetime. This approach is mainly critiqued on grounds that viewing health as only having value in adding to "national output" is not consistent with welfare economics [28]. It also reflects underlying societal discrimination (such as racism and sexism – see footnote 2).

The cost-benefit approach is mainly criticised on grounds of the problems associated with these methods used to ascribe monetary value to 'health' or human life [108, 111, 117].

2.5: COST EFFECTIVENESS ANALYSIS

Cost-Effectiveness analysis has been the most prevalent type of economic evaluation of health care [28, 32]. It involves the measurement of benefits (or outcomes) in terms of units of health outcomes, or intermediate outcomes such as cases treated [32, 96]. This approach requires that the outcomes of a health intervention be measured in quantitative units (number of cases treated, life years saved, etc), or utility. The criterion for choosing which intervention is worth implementing is the relative cost-effectiveness ratios (C/E) of the alternatives, where the intervention with the lowest C/E ratio would be the most 'cost-effective' and hence the most desirable [32]. A major criticism against the CEA method is that there is no explicit indication of whether an intervention should be implemented, as having the lowest C/E ratio does not necessarily mean that the intervention is 'worth' implementing.

2.5.1: Measuring Costs in CEA

Costing involves the identification, quantification and valuation of all resource changes associated with a given health intervention [108, 118]. It is generally recommended that when considering a societal perspective, resources should be valued at an amount equal to their opportunity cost [118-120]. Consideration of the broad societal perspective implies that all

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[6] Robinson (1986) quotes an example of the work of Cooper and Brody (1972) where, using a 2 per cent discount rate, the value of a college educated 'white' man high school dropout was estimated at US $ 475,000 and his 'black' counterpart at US $ 165,000. The estimates for 'white' and 'black' women of the same age and level of education were US $ 140,000 and $ 108,000, respectively.

resource and outcome changes should be included in an evaluation, regardless of who incurs the costs and who gains. The choice of costing perspective, however, depends on the questions an evaluation seeks to answer. In this study, costing was undertaken from the public provider's perspective because the main objective of the evaluations was to assess whether the change from monotherapy antimalarials to ACTs was a cost-effective, within the context of free health services for the management of malaria and where more than 95% of the people sought malaria treatment from a public health facility.

In a competitive market, prices of commodities reflect their opportunity costs. In the health care market, however, there are no market-clearing prices; hence caution needs to be exercised when attaching value to cost items. The level of detail of costing is determined by the aim of the study. Studies seeking to provide global conclusions can undertake 'gross-costing', an approach that is less time-consuming and provides better opportunity for generalising, but with less precision. 'Micro-costing', on the other hand, is more detailed and time consuming but provides results with better precision, and is the recommended approach to costing in general [118, 121]. Generally, it is recommended that *average costs* be used in economic evaluations, especially where generalisation of cost consequences to a national level is necessary [118]. In this study, micro-costing was used based on data from an adequate number of health facilities that were representative enough to allow for conclusions to be drawn for the entire province in which the study site was situated.

The time horizon of an evaluation is of critical importance to the future cost consequences of an intervention. It is recommended that an appropriate choice of a time horizon, as well as well as the estimation of costs that may occur beyond this period be made Future costs can be collected through further collection of data, after the initial study period, or through modelling [118, 121]. Although the effects of using ACTs for managing uncomplicated malaria are expected to be fairly long-term, both in terms of reducing malaria transmission and in delaying the onset of resistance to the different drug components of the ACTs, the estimation of long-term effects of ACTs were beyond the scope of this study. Only short-term (2-year) effects were evaluated.

Textbooks on economic evaluation identify various categories of resources that should be included in the calculation of an intervention's costs, which include, depending on the costing perspective; [118, 121]

- ★ health care resources
- ★ non-health care resources
- ★ informal caregiver time
- ★ changes in use of patient time (for treatment)
- ★ future costs that are a consequence of the intervention

2.5.2: Identifying, measuring and valuing health outcomes in CEA

Over the years it has become essential to demonstrate quantified improvements in health (or well-being) in order to justify the cost of achieving it. This has posed analysts with the challenge of quantifying the increase in "well being" by measuring 'quality of life' in addition to measuring its length. Unlike the CUA and CBA approaches where health outcomes are expressed in a measure of utility and in monetary terms, health outcomes in a cost-effectiveness analysis are measured in natural units which could be final outputs such as, life years gained or deaths averted, or intermediate outputs such as cases treated or positive cases detected. The choice of which unit to use depends on the objectives of the intervention(s) being evaluated [108]. Such objectives should be made clear upfront. In the case of the studies presented in this thesis, the main objectives was to establish whether the switch from SP monotherapy to ACTs in the South African sites was cost-effective so as to inform decision-making in other South African sites (particularly Limpopo province) and neighbouring countries. In addition, the study on RDTs aimed to provide information to Mozambique on whether scaling up of the implementation of RDTs would be a cost-effective option. Given these objectives, the health outcomes chosen for the CEA of ACTs in Kwazulu Natal and MPUM are (a) *malaria cases successfully treated* and (b) *malaria cases averted*. For the CEA of RDTs, the health outcome measure chosen is *malaria positive cases treated*.

2.5.3: Calculating effectiveness and cost-effectiveness ratios

In a cost-effectiveness analysis, the cost-effectiveness ratio is made up of a numerator (difference in costs of two interventions) and the denominator (difference in effects of the interventions). The **cost-effectiveness** (C/E) **ratio** expressed as incremental costs divided by incremental health effects/benefits is the guiding factor for decision-making. This *incremental C/E ratio* (ICER) is defined as the "*incremental price for obtaining a unit health effect from a given health intervention when compared to an alternative*" [119, p.27]. The decision rule in CEA is based on this ICER, where an intervention whose ICER is less or equal to a given value is considered 'cost-effective' and hence is worth implementing [38, 41, 42, 119, 122-124]. Standard practice in CEA particularly encourages the use of *incremental cost-effectiveness ratios* (ICER), as opposed to *average cost-effectiveness* ratios (ACER), as the basis for decision rules that guide resource allocation decisions [124]. The *effectiveness* of an intervention can be simply defined as the extent to which it achieves health improvements in real practice settings [125].

The ICER of two interventions A (the intervention currently in place) and B (the new intervention) is defined as: [38, 39, 41, 123, 126]

$$ICER = (\mu_{CB} - \mu_{CA})/(\mu_{EB} - \mu_{EA}) \quad (1)$$

Where μ_{CA} and μ_{EA} represent the *population* mean cost and mean health effect of intervention A, respectively, and μ_{CB} and μ_{EB} population mean cost and mean health effect of intervention B, respectively. Since most true population mean costs and health effects are unknown, analysts calculate the ICER based on estimates of mean costs and health effects from a sample of patients. This is particularly true for **stochastic CEAs**, usually based on patient-level data collected as part of randomised control trials or observational studies [39]. Using the sample means of costs and health effects brings some degree of uncertainty due to sampling variation, and as such results in the need to report some kind of confidence interval for the ICER point estimate [38, 39, 123]. Point estimates of ICER do not provide sufficient information for decision-making. This is particularly the case when no further information is available about the quadrant (see Figure 2.1 below) in which the CE ratio falls. This is one of the major drawbacks of ICE ratios, and it poses difficulties in the calculation of confidence

intervals for ICERs. ICER point-estimates can be analysed using the CEA plane, as presented below. From Figure 2.1, the CEA decision rule for quadrants II (B 'is better than' A) and IV (A 'is better than' B) are straightforward. In contrast, the decision rules for quadrants I and III are not straightforward and are defined as [38, 39, 126]:

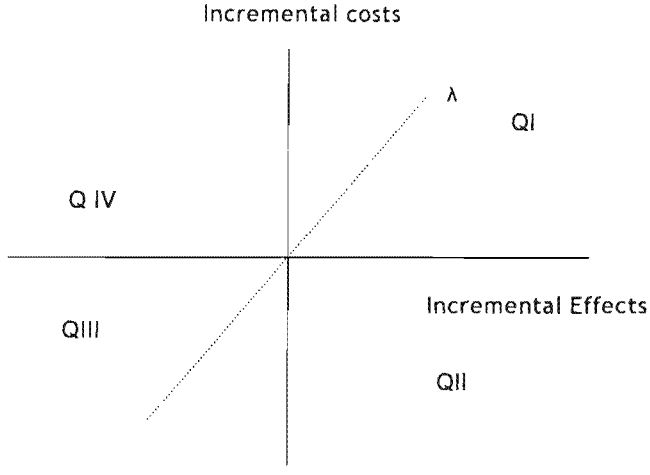


Fig 2.1: Cost-effectiveness Plane

QI: B 'is better than' A, if and only if ICER ($\Delta C/\Delta E$) < λ
QIII: B 'is better than' A, if and only if ICER ($\Delta C/\Delta E$) > λ

where λ is the maximum willingness to pay for an additional unit of health gain or the threshold C/E ratio.

2.5.4: Discounting costs and health benefits

The impact of health interventions, in terms of both costs and health effects, usually occurs in a period longer than one year and normally beyond the timeframe of any study design. This means that the evaluation of future costs and health effects need to be converted into their present values, by discounting them at some rate(s) of interest [127-129]. Inter-temporal aspects of decision-making form the basis for discounting, in the sense that individuals make decisions (about investment, health, education, etc) in the present time with knowledge that some of these decisions provide immediate benefits, while the benefits of other decisions are achieved in the future. The extent to which individuals make decisions that postpone their 'enjoyment' into the future depends on how much importance they attach to these future benefits. Generally, an individual would prefer to receive $10 now than receiving $10 one year

later, implying that different weights are attached to 'enjoyment' now and 'enjoyment' in the future. There is consensus that future costs of health interventions should be discounted in order for them to be expressed in present terms [119, 127, 130]. The only source of debate on the issue of discounting costs is around the discount rate to be used. Even then, there seems to be consensus that a discount rate of 3% - 5% is most appropriate and these rates have been widely used in economic evaluations [108, 127]. A *temporal discount rate* is an indicator of the extent to which a person diminishes the value of a future outcome [131]. From a societal viewpoint, decisions made today have implications for both current and future generations. For example, benefits consumed in the present period are a trade-off that excludes the future generation from consuming them. Determining a social discount rate, thus, tries to address concerns about the extent to which governments should allocate resources to promote the welfare of the current generation as opposed to future generations. A low discount rate reflects a greater orientation towards future benefits, and vice versa.

An important distinction to make is that of *intra-generational* and *inter-generational* discounting [128-130, 132]. Van Hout (1998) argues that discount rates should be estimated based on the expected growth rates of costs and health effects and their elasticities regarding the social utility function. He emphasises the need to take into consideration both current and future generations when making decisions about discounting. Gravelle and Smith (2001) also emphasise the need to make a distinction between effects happening to individuals who will be aged *a* in periods t and t+1 (inter-generational) and effects to those who will be aged *a* and *a+1* in period t+1 (intra-generational). They highlight the possibility of using different discount rates for different time periods, that is, for each stream of benefits to be discounted to their own present value using individuals' preferences and a social discount rate. Hence, the use of different discount rates for different time periods "provides a neat method for reconciling respect for individual preferences over decisions that affect them directly with a social concern for inter-generational equity" [132, p.592]. The issue of discounting becomes more critical in the case of evaluation of interventions for mitigating the impact of drug resistance (as is the case for this study) where the impact of the intervention is lagged and hence the choice of a discount rate needs to take into consideration the preferences of future

generations (which are currently not known). Smith and others particularly note that it is important to consider the influence that discounting may have on the choice between policies that affect transmission of resistance and those that affect the selection pressure for the development of resistance to antimalarials [133].

A substantive amount of literature exists around discounting and how to estimate discount rates [127-132]. In particular, the estimation of a social discount rate has received a lot of attention. The literature consists of two broad approaches for the estimation of a social discount rate, namely; *revealed preference* in the marketplace and *stated preference*. Under the revealed approach, the *social opportunity cost* (SOC) and the *social time preference rate* (STPR) have been identified as methods of estimating a social discount rate [128-130].

There is controversy on whether health effects should be discounted. Although there is general consensus around the need to discount costs in economic evaluations, there has been a fairly substantive debate around discounting health effects. This debate has mainly been around three aspects [127-132]:

(a) Should health effects be discounted?

(b) If yes, what discount rate should be used for health effects?

(c) Should costs and health effects be discounted at the same rate?

Generally speaking, there are three broad propositions about discounting health effects. While some authors argue that health effects should not be discounted at all [134, 135]; others demonstrate that health effects should be discounted at a rate lower than that used to discount costs [129], and yet, others argue that both costs and health effects should be discounted at the same rate [128]. Authors like Gravelle and Smith (2001) argue that health effects should be treated differently, depending on the units in which they are expressed. They propose that in cost-benefit analyses, where health effects are expressed in monetary terms, both costs and health effects should be discounted at the same rate, while in cost-effectiveness analyses, where health effects are expressed in natural units, health effects should be discounted at a rate lower than that used for costs [132].

To date, the practice of whether or not to discount health effects at the same rate as costs seems to be influenced by whether or not one is a 'believer' or 'non-believer' in market forces [129, 130]. However, in some countries, specific guidelines have been developed. For example the US panel on Cost-effectiveness explicitly recommends that both costs and health effects be discounted at the same rate [128], while the Department of Health (UK) recommends a discount rate between 1.5 – 2 percent for health effects and 6 per cent for costs [130].

2.6: ECONOMIC MODELLING

2.6.1: Introduction

One of the key concerns about measuring health outcomes, as noted by Detsky, is that for most health interventions 'health outcomes' are only achievable in the very long run [136]. Cropper and Sussman (1990) also highlight this point when they argue that some of these lagged effects are borne by both current and future generations. Given this, analysts need to find a method for extending the evidence of effectiveness to cover the time interval for which effectiveness could logically apply. The issue of lagged effects brings to the fore the importance of discounting benefits accruing to future generations [127-129] discussed earlier. It is possible to estimate effects that usually extend beyond the timeframe of a trial using complex decision-analytic models. Decision-analytic models are increasingly becoming part and parcel of economic evaluation [15, 49, 137-139], not only as predictive tools to estimate lagged effects, but also as tools that provide synergistic contribution to the techniques of economic evaluation. In particular, modelling is helpful in dealing with uncertainty [138-142], dealing with the problem of data gaps and unknown facts [138, 139, 143, 144], and is also useful in synthesising data for meta-analyses [139, 140, 145].

Modelling has been defined as "a way of representing the complexity of the real world in a more simple and comprehensible form" [138, p.2]. Modelling can be defined as the systematic structuring of relationships between variables in order to create a simplified replica of the particular phenomenon of interest. Smith and others describe it as the extrapolation of the

main parameters that influence a phenomenon of interest, and then the construction of relationships between these parameters [133]. Modelling is a tool used for 'measuring' the influence of the occurrence of certain events on a particular outcome of interest. In economic evaluation, modelling is "a systematic quantitative approach for assessing the relative value of one or more decision options" [145, p.20]. The process of modelling involves defining and bounding of a problem of interest, structuring of the problem by developing an appropriate model, gathering data and analysing the model [145].

Models employ an analytic methodology to account for events that occur over time. Models can be either *deterministic* (where the average number of events per population is used) or *stochastic* (where randomisation is used to simulate the probability distribution of events that may occur) [33]. Models may apply to cohorts longitudinally or to populations cross-sectionally. Health outcomes in longitudinal cohort models are calculated on the basis of homogeneous cohorts that are followed for a period of time. On the other hand, in cross-sectional studies the model tracks the health outcomes in a population in each period and sums across time to estimate aggregate measure of health outcomes. Such population models are best suited to modelling heterogeneous populations and when measures of aggregate effectiveness and/or cost are desired [33].

2.6.2: Role of modelling in economic evaluation

The use of models in cost-effectiveness studies has been increasing over the years despite the concerns and debates about the role of modelling in economic evaluations [138-140, 146]. For example, Goodman and others, on the basis of economic models, use secondary data to evaluate the costs and cost-effectiveness of different malaria control strategies in different settings [27]. While their findings were good as a starting point for policy debates, they cannot form the basis for decision-making in a specific country. Economic evaluations based on modelling face the limitation of relying on assumption (in the absence of data) and are thus criticised on grounds of using unrealistic assumptions, as well as being difficult to assess due to ill-defined methodologies. Nevertheless, the need to use modelling in economic evaluation remains of critical importance. For instance, Wilkins and others provide valuable information

on the costs and cost-effectiveness of chloroquine and sulphadoxine-pyrimethamine in South Africa [146]. Based on the results of a decision-tree model, they find that using SP for first line treatment of malaria was 5-times more cost-effective than using chloroquine, despite the 20-fold lower cost of chloroquine. This finding is of importance in highlighting the fact the lower price of a drug does not necessarily always mean that it is cost-effective. Similarly, Sudre and others use a decision-analytic model to evaluate the costs and cost-effectiveness of chloroquine, amodiaquine and SP in African children [147]. They arrive at a similar finding as that reported by Wilkins and others [146], that despite being of a higher cost (45% more compared to cost of chloroquine), SP was the most cost-effective treatment [147]. They conclude that decision analytic models are useful tools in economic evaluations, despite their limitations.

Buxton and others classify the uses of models in economic evaluation as follows: [138]

(a) Extrapolating beyond the date observed in a trial. Clinical trials usually report data on clinical outcomes for a period of time of the trial (usually relatively short-term), while economists are usually interested in long-term health outcomes such as life years saved. In order to derive these long-term outcomes, some extrapolation of the short-term data is required.

(b) Linking intermediate clinical outcomes to final health outcomes. This is especially necessary in situations where final health outcomes take many years to manifest themselves. It is possible to compare interventions using data from trials; however, this would be inappropriate for interventions that have long-term effects, especially if the relationship between the intermediate endpoints and the long-term health outcomes is not necessarily linear.

(c) Generalising to other settings. Clinical trials are normally conducted in 'controlled' settings and hence may not represent 'real-world' conditions. Economic analysts are normally concerned with what findings of clinical trials mean in practice and whether economic evaluations based on such findings have the same 'economic implications' for different contextual settings.

(d) Informing decisions in the absence of hard data. Modelling is useful when there are data gaps for key variables (e.g. when experimental observation is not possible – for example experimenting with natural phenomena like earthquakes). Also, models serve to identify priorities for further data collection.

2.6.3: Approaches to modelling in economic evaluations

Decision-analytic models used in economic evaluation include, decision trees, Markov models, Monte Carlo (stochastic) simulations, and Discrete Event simulations. The most commonly used approaches are decision trees [27, 146, 148] and Markov models, and will be briefly described below.

Decision Tree models

A decision tree "*graphically depicts components of a decision problem and relates actions to consequences*" [145, p.21]. Decision trees are the simplest models to build, maintain and understand. About 57% of studies on modelling within the pharmaceutical industry have used decision tree models (Andy Dugan, Modelling Specialist at Oxford University, *personal communication*). Decision trees provide a simple way of structuring and analysing decision problems. Each strategy being evaluated is described by one branch from the initial decision node. Branches at relevant chance nodes represent the pathways for patients, in a linear sequence of probabilistic movements towards the endpoints of the tree. These movements take place over a fixed period of time [145]. However, because of their simplistic nature, decision trees quickly become too unwieldy when used to analyse complex decisions [145, 149]. For example, situations where events occur more than once within a period of time can be presented by adding branches at every chance node (where an event could occur). This would permit the recurrence of events (as might be true for certain disease conditions). However, such recursive trees would become too 'bushy' even for a very short time horizon [149]. Therefore, given their static nature, decision trees are inappropriate for assessing problems that recur and that run over a long period of time [149].

Markov modelling

Markov models are the second most commonly used models in economic evaluations. Within the pharmaceutical industry about 23% of the published work has used Markov models (Andy Dugan, *personal communication*). A Markov model is a decision-analytic model that involves a Markov process. "*A Markov process is a modelling technique derived from matrix algebra, which describes the transitions a cohort of patients make among a number of health states during the series of short or long cycles*" [136, p.125]. Markov models are particularly appropriate for diseases in which events can occur repeatedly overtime.

The recursive nature of the Markov models allows for dynamic occurrence and recurrence of events at any point within the time horizon. Markov models are particularly useful when a decision problem involves risk that is ongoing over time. Their dynamic nature also takes into consideration (1) the fact that the times at which events will occur are uncertain, and (2) the fact that a given event may occur more than once [149]. The basic structure of a Markov requires that patients be in only one of the finite *health states* at a given point in time. Markov health states must be mutually exclusive but collectively exhaustive. All events in a Markov are modelled as transitions from one state to another. At fixed increments of time (known as *Markov Cycles*), people transit among health states according to a set of *transitional probabilities* [140, 149, 150]. At any point in time, the people in a given health state are not distinguishable from one another (both in clinical attributes and in previous disease history). The *Markovian assumption* states that the transition probabilities depend only on current health states and not on past health states that an individual could have gone through [140, 149, 150]. This is one of the major limitations of Markov models. However there are ways of overcoming this shortcoming, which include the use of "tunnel states" or the use of more health states within a model such that each health state represents a unique health-state history. The greater the number of health states used in a Markov model, the more complex the model becomes and such complexity also implies more data needs.

Markov models can be analysed using Cohort simulation (which tracks a hypothetical cohort

of patients simultaneously through the model) or the Monte Carlo simulation (which randomly selects a patient from a hypothetical cohort, and each patient transits through the model at one time).

2.7: ECONOMIC EVALUATIONS OF MALARIA CONTROL INTERVENTIONS

Although there has been a lot of literature on malaria (in general), there is limited literature on the economic evaluation of malaria control interventions. In their review conducted in 1999, Goodman and others report that they were able to find 16 economic evaluation studies of various malaria control strategies in sub-Saharan Africa [27]. Fifteen of these studies were cost-effectiveness analyses and one was a cost-benefit analysis study. Interventions reviewed included insecticide-treated nets, indoor residual spraying, chemoprophylaxis in children and pregnant women, and malaria treatment (*ibid*). They report that no cost-effectiveness studies were found for other interventions such as environmental management, untreated nets, case management of severe malaria, treatment outside the formal health care system, the control of malaria epidemics, and other methods of personal protection. The methodologies used in these economic evaluation studies varied; some used mathematical models while others were based on data collected during trials, costed either prospectively or retrospectively [27, 68]. Subsequently, a few further economic evaluation studies on malaria control strategies have been undertaken [151, 152]. The Institute of Medicine, using models, evaluated the consequences of 'not treating' (i.e. continuing to treat with an ineffective antimalarial) and those of changing to ACTs. Under the assumptions of their model, they report that for children under 5 years, treating with ACTs saves lives at less than $8/DALY (with presumptive treatment) and $6.23/DALY (with definitive diagnosis using an RDT) [151].

There has been more economic evaluation of malaria prevention interventions, particularly of insecticide-treated nets than there has been of malaria case management. In their review, Goodman and others rated evaluations of ITNs, residual spraying and chemoprophylaxis as having 'fair' or 'good' data on both costs and effectiveness data, and rated change of first line treatment, improvement in diagnosis and the use of combination antimalarial therapies as having 'very limited' or 'no' data on costs and effectiveness [27, p.14]. The studies presented

in this thesis are focused on 3 malaria interventions namely, indoor residual spraying, malaria case management using ACTs and routine use of definitive diagnosis using RDTs. Hence, emphasis will be put on review of literature specific to the economic evaluation of these interventions.

Literature on the evaluation of IRS shows that the cost-effectiveness ratio is dependent on several factors including: whether or not malaria transmission is seasonal or not, the type of insecticide used for spraying, the number of spraying rounds per year, and whether or not spraying is done in very low or middle income countries/settings [27, 68, 153]. For a very low income setting, Goodman and others reported CER (cost per DALY) for 4 different insecticides: DDT $18 ($13 - $ 24), Malathion $20 ($15 - $27), Deltamethrin $21 ($15 - $28) and Lambda-cyhalothrin $22 ($16-$29) [27]. Results of their evaluation show that the CERs of evaluations for the very low and middle income settings are not significantly different but they are substantively differently from the CERs in a higher income settings [68].

Improving malaria diagnosis is one of the critical strategies for improving malaria case management [2, 57, 58, 154, 155]. While a lot of research has gone into the evaluation of malaria diagnostic tools in field trials, very limited research has been undertaken to evaluate the cost-effectiveness of definitive malaria diagnosis as a part of malaria case management. Goodman and others' evaluation of definitive diagnosis focused on treatment using the traditional cheap antimalarials (CQ, SP and AQ) and on a narrow perspective of drug cost savings per patient only, it is not surprising that they reached a conclusion that "*it is apparent that the use of additional diagnostic technology is very unlikely to be cost-saving in SSA because the current first line drugs are relatively inexpensive drugs*" [27, p.126]. They suggest that RDTs would be cost-saving where the average drug cost per treatment course is $1.97 and $2.87 in low and high transmission areas, respectively (*ibid*).

As noted earlier, there is limited literature on the economic evaluation of change of first line treatment of uncomplicated malaria [27, 44, 49, 148]. The results of the economic evaluation of changing first line treatments are dependent on the effectiveness and price of drugs being

evaluated, patient adherence to treatment, malaria transmission patterns, the effectiveness of other malaria control strategies and the timeframes considered for the evaluation. A key challenge to the economic evaluation of antimalarials, in light of drug resistance, is the high degree of uncertainty around the development and rates of growth of resistance to specific antimalarials. Goodman and others report that the use of ACTs is potentially cost-effective in high transmission areas, but this is dependent on the extent of the reduction in the growth of resistance to SP [27]. The few cost-effectiveness studies on malaria case management have recently focused on evaluating artemisinin-based combination drugs in comparison to the traditional monotherapy antimalarials [15, 152]. For example, Coleman and others conducted a threshold analysis of ACTs in sub-Saharan Africa [152]. Due to the uncertainties around the rate of development and spread of resistance to ACTs, Coleman and others relied on using economic modelling techniques to model health outcomes associated with the use of ACTs in the long-term. In their study, Coleman and others conclude that ACTs are more than 95% likely to be cost-effective under most conditions.

Most household-based studies on malaria focus on estimating the burden of disease and/or documenting the relationship between malaria episodes and socio-economic status. Several studies have documented the burden of disease in terms of costs (both direct and indirect) incurred by the households during a malaria episode as well as the strategies that households use to cope with the burden (both financial and lost productivity time) [52-54, 156], as well as the cost to countries (in terms of hampered economic growth) [9, 157]. Where both direct and indirect costs have been estimated, the indirect costs of malaria always exceed the direct costs. In addition, studies undertaken at household level have shown that there is a relatively higher economic burden of malaria for poorer households compared to the richer households. Asenso-Okyere and Dzator estimated direct and indirect costs of malaria in Ghana. They reported a total cost per malaria case was equivalent to US$8.67 in 1993. This is equivalent to 4.7 days of agricultural wages for a woman and 3.7 days of wages for a man [52]. From a survey of 1,038 households, Attanayake and others report a value of lost income of US$7.5 on average per economically active patient [53]. Most household studies on malaria report the same coping strategies for households during a malaria episode. These coping strategies

include: incurring debt to cover the costs of malaria, postponing seeking care until the symptoms became severe, reallocating finances, food supplies and work routines, and labour substitution among household members in attending to the productive work of, and in caring for, the patient [52-56],

2.8: CONCEPTUAL FRAMEWORK

2.8.1: Introduction

This section describes the conceptual framework within which the 'cost-effectiveness' of ACTs and RDTs will be evaluated. Based on the literature review, this section seeks to develop a framework for identifying central issues concerning costing methodology and the methods for measuring health outcomes associated with ACT. The evaluation framework of this study seeks to clarify issues important to cost-effectiveness analysis and to provide a basis for developing this study's methodology.

In order to understand the framework within which ACT will be evaluated, let us consider a brief summary of the consequences of resistance to antimalarials, the need for change to and the expected benefits of artemisinin-based combination drugs.

It becomes imperative to change to a more effective drug when the current drug becomes ineffective in the treatment of a particular disease. In the case of malaria, an ineffective first line drug has serious implications from public health and efficiency viewpoints. Firstly, increasing levels of drug resistance result in increasing risk of treatment failure (which, in turn results in prolonged illness, recrudescence of uncomplicated malaria or progressing to severe disease). These adverse health outcomes have several impacts at health facility and household levels. An increasing number of malaria cases results in a higher caseload at health facilities, hence increasing the pressure on the frequently already weak and insufficiently funded health care infrastructure, particularly in the countries where malaria burden is highest. Secondly, increasing antimalarial resistance fuels increased malaria

transmission due to increasing the gametocytes pool in the community, particularly with resistant parasites. This increased malaria transmission results in a further increase in malaria cases. Moreover, more of the drug-resistant parasites get transmitted over time. Apart from the negative health outcomes associated with resistance, there are cost-related implications. Obviously, increased malaria cases and hospitalisation result in increased costs (direct and indirect) for both households and providers of health care services. Moreover, being ill with malaria also results in productivity losses.

Certainly, there comes a point where the first line drug has to be changed, and this will usually result in costs related to implementation of the new treatment policy (including, acquisition cost for the new drug, cost of removing the old drug from the system, cost of changing treatment guidelines, and cost of re-training health workers). At a global level, the problem of increasing drug resistance results in a need for new research and development of new more effective (but hopefully affordable) antimalarial drugs.

It is hypothesised, based on evidence from Thailand and South Africa [24, 158], that ACTs will have a multifaceted impact reducing malaria morbidity and mortality, thus limiting the impact of resistance to antimalarials. However, concerns about costs, sustainable affordability and availability of ACTs remain an obstacle to its widespread implementation. In light of this, there is need for comprehensive evaluation of cost-effectiveness of ACTs in specific contextual settings, so as to make informed choices on which antimalarial to use for first line treatment.

2.8.2: Analytic framework

Despite the expected impact of ACTs described above, it remains essential to quantify and value the expected benefits and costs associated with their implementation, and to compare these with the costs and potential benefits of current first line antimalarials. In broad terms, the key question regarding the evaluation of ACTs is: *Can an economic case be made that the introduction of ACTs would improve society's welfare?* The decision to change first line treatment policy for malaria is faced with policy questions such as:

- ★ At what level of treatment failure with an existing drug should policy be changed?
- ★ What alternatives should be considered for the new policy?
- ★ What is the best option, within a given context, among a range of alternatives?
- ★ What will new treatment policy cost? Will it be more expensive than current policy?
- ★ Would the new treatment policy be cost-effective? Would it be cost-effective in the absence of other malaria control strategies (e.g. effective vector control)?
- ★ Does definitive diagnosis of clinically suspected malaria cases before treatment add any value?

Specifically the following questions are critical in the evaluation of ACTs for the studies presented in this thesis:

- ★ Within the context of effective vector control, routine use of definitive diagnosis before treatment and a well regulated supply of antimalarials, are ACTs more cost effective than monotherapy antimalarials?
- ★ What is the more cost-effective alternative between AS+SP and AL?
- ★ What is the role of vector control, as an approach to malaria control?
- ★ What is the role of definitive diagnosis when ACTs are used for first line treatment?

The evaluation of the change in malaria treatment policy in South Africa in this study has been undertaken in the following contextual setting:

- ★ Low intensity malaria transmission
- ★ Effective and improved vector control strategies in study site and neighbouring areas
- ★ Well established health infrastructure and competent organisations to implement and supervise change in treatment policy as part of routine activities.
- ★ Well regulated pharmaceuticals
- ★ Use of routine definitive diagnosis before treatment (in South Africa but not in Mozambique)
- ★ High treatment seeking behaviour in public sector and high compliance rates to antimalarial treatment

The cost-effectiveness approach provides a framework to evaluate the use of ACTs in Kwazulu Natal and Mpumalanga and the implications of routine use of RDTs before providing antimalarials in Mozambique. The ICER has been used to assess the relative cost-

effectiveness of the interventions evaluated. Unit cost measures for malaria outpatient and inpatient services considered include:

- ★ Cost/ malaria case averted
- ★ Cost / malaria case successfully treated

The evaluation of limiting ACT use to patients with malaria diagnosis confirmed by RDTs in southern Mozambique in this study has been undertaken in the following contextual setting:

- ★ Previously high intensity malaria transmission, rapidly being reduced through the recent introduction of community based indoor residual insecticide spraying programme
- ★ Relatively high treatment seeking behaviour in public sector (as a result of very limited private health care facilities in the study area)
- ★ Basic Primary Health care Infrastructure focused on the provision of key essential medicines for the treatment of common conditions
- ★ Clinical diagnosis of malaria, primarily based on the presence of fever
- ★ Reasonably high compliance rates to antimalarial treatment

The evaluation of ACTs and RDTs in the studies discussed in this thesis is based on data collected for a short timeframe (1-2 years). A true reflection of the impact of ACTs and RDTs requires a broad consideration of a longer timeframe and all aspects of the effect of these interventions. Due to time constraints, the evaluations discussed in this thesis have only been focused on specific aspects of ACTs and RDTs, and have not addressed all areas of potential impact of these interventions. For example, longer-term evaluation of these interventions is beyond the scope of this thesis. Similarly, comprehensive and aggregated impact of the interventions, such as the benefits of early diagnosis (and hence provision of appropriate treatment) of febrile cases found not to have malaria has not been studied in this thesis.

It can be argued that the synergy of various malaria control approaches would most likely result in improved reduction in the malaria burden. In 2000, Kwazulu Natal simultaneously improved its vector control and malaria case management strategies and also directly

benefited from the vector control strategies recently implemented in southern Mozambique,. Although Mpumalanga also changed their first line treatment policy, and might have benefited (to a lesser extent) from the introduction of vector control strategies in southern Mozambique, their vector control strategy did not change. Evaluating the impact of AL in Kwazulu Natal requires the careful consideration of the role and contribution of vector control to the observed reductions in malaria cases, admissions and deaths. Comparisons of findings from Kwazulu Natal and Mpumalanga, extensive sensitivity analyses as well as the Delphi estimates of contributions of each malaria control strategy will be used for identifying the role of vector control in Kwazulu Natal.

The broader relevance of the findings of the cost-effectiveness analyses undertaken in will be discussed, taking into consideration the specific contextual issues in the study sites. Most important of these are the role of effective indoor residual spraying. Other important contextual issues include: malaria transmission rates, existing health care infrastructure and malaria control programs, treatment-seeking behaviour in the private sector (especially for the treatment of malaria) and pharmaceuticals regulation and control.

2.9: CONCLUSION

The salient points, derived from the literature, that are relevant in informing this study's conceptual framework and methodology include the following:

- ★ Current efforts and initiatives used in the control and management of malaria, a disease with one of the highest global burden, are becoming severely challenged by the evolution and rapid spread of resistance to both antimalarials and residual spraying insecticides. With 'prompt effective treatment' being the most fundamental strategy for malaria control as well as malaria case management, there is a need to find mechanisms that will contain the emergence and spread of resistance, especially to relatively affordable antimalarial drugs currently available.
- ★ The use of combination antimalarial therapy, especially the artemisinin-based combinations, has demonstrated the potential to delay the emergence and spread of

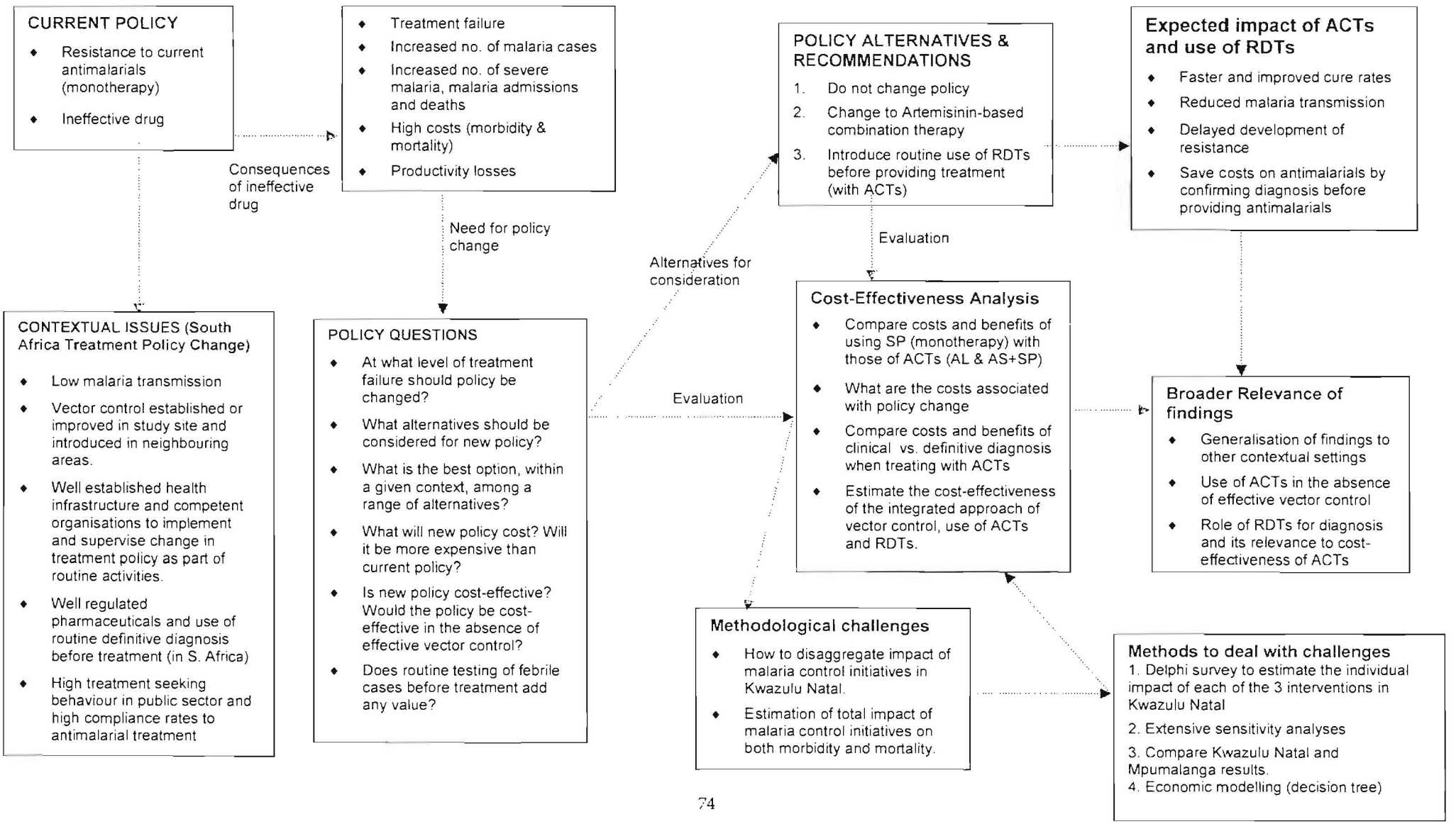
resistance and reduce transmission of malaria, while simultaneously providing rapid-acting and effective treatment.

- ★ An integrated approach to malaria control that includes strategies on improved case management, effective indoor residual spraying and routine use of definitive diagnosis before providing antimalarials results in larger reductions in the malaria burden (both in terms of morbidity and mortality) and has the potential to be cost-effective.

- ★ The application of economic evaluation techniques to the complex field of malaria case management is ambitious but essential. Cost-effectiveness analysis (CEA), despite its flaws, can be used in the evaluation of strategies aimed at improving treatment outcomes and ensuring malaria control. In particular, the synergistic approach that combines cost-effectiveness analysis and modelling is essential in addressing some of the methodological limitations of the CEA approach.

- ★ In contexts where the measurement of the impact of one intervention is difficult, the use of the Delphi technique is a possible option, if the Delphi survey is well designed.

Summary of Conceptual Framework



3. METHODOLOGY

3.1: BACKGROUND

The South-Eastern Africa Combination Antimalarial Therapy (SEACAT) study, which commenced in 2000, had a broad objective to evaluate the introduction of ACTs in Mozambique, Swaziland and South Africa. The SEACAT study was designed as a long-term comprehensive evaluation with several components including, in-vivo, drug utilisation, gametocyte carriage, and economic evaluation studies.

The economic evaluation studies of artemisinin-based combination therapies (ACTs) were undertaken in three study sites in South Africa, namely Kwazulu-Natal, Mpumalanga and Limpopo (previously Northern) provinces; two study sites in southern Mozambique, namely Namaacha and Matutuine; and in one study site in Swaziland. The information presented in this thesis forms only part of the economic evaluation studies done as part of SEACAT project. Specifically, this thesis does not include the costs and cost-effectiveness analyses for other SEACAT sites (i.e. Limpopo province in South Africa, Swaziland, and the cost-effectiveness of ACTs in Mozambique). I was the principal investigator on the economic evaluation component of the SEACAT study, charged with the responsibility of designing the study methodologies and data collection tools, collecting and analysing data and writing regular research project reports. I was involved in designing the household survey questionnaire used in all the SEACAT sites, training and supervising data collection with the surveys in Kwazulu Natal and Mpumalanga, as well as preliminary analysis of the household survey data from these two sites. From the outset, it was expected that some of the research work would feed into this thesis, as part of the capacity building part of the SEACAT study. A research intern at the Health Economics Unit assisted with data entry once it was collected and usually travelled with me during the data collection phase. A senior researcher at the Health Economics Unit provided me with technical and overall guidance on this research project, while the overall SEACAT principal investigator provided technical guidance on matters relating to malaria and its control interventions. My contribution to the SEACAT project is that of being the principal investigator responsible for data

collection, analysis and writing on the economic evaluation studies. The analyses presented in this thesis were based on data that I collected on the SEACAT project. These analyses have been undertaken solely for purposes of the PhD thesis. The write-up of the results presented here has not been done elsewhere for other purposes or fora.

Figure 3.1: Map showing the SEACAT study sites (Kwazulu Natal, Mpumalanga, Limpopo [previously Northern Province], Swaziland and Mozambique).

The focus of this thesis is limited to the cost-effectiveness analysis of ACTs in only two study sites in South Africa (Kwazulu Natal and Mpumalanga) and the cost-effectiveness of RDTs in southern Mozambique. Due to the time constraints related to the completion of the thesis and the delay in implementing ACTs in Limpopo, Mozambique and Swaziland, evaluations of ACTs in other study sites have not been included in this thesis. The economic evaluation of ACTs has taken a "before and after" approach, which involves collection, analysis and comparison of baseline data (with SP monotherapy as a first line drug) and of post-intervention data (with ACTs as first line drugs for malaria treatment). Baseline data for both study sites were collected in 2001 for the same year (2000). Since the implementation start dates of the new policies were different, post-intervention data for Kwazulu Natal were collected in 2003 for the year 2002 (AL having been implemented in January 2001), and post-intervention data for Mpumalanga were collected in early 2004 for the year 2003 (AS+SP having been implemented in January 2003). This evaluation of ACT over a short period of time (1-2 years) was undertaken. In spite of some contextual differences (see Table 3.1), the methods for collecting and analysing data were standardised across all the SEACAT sites, including Kwazulu Natal and Mpumalanga. A description of the methods applicable to a specific study site is presented in the respective results chapters, while the general methods across all sites are described in this chapter. The methods used in the evaluation of rapid diagnostic tests in Mozambique are covered in chapter 6. The key differences between Kwazulu Natal and Mpumalanga are presented in Table 3.1.

Table 3.1: Key differences between Kwazulu Natal and Mpumalanga

	Kwazulu Natal (KZN)	Mpumalanga (MPUM)
Malaria Transmission	Low intensity (EIR < 1), seasonal malaria transmission	Very low intensity (EIR < 0.1) seasonal malaria transmission
Vector control activities	IRS activities date back to 1950s. However, in 2000, the resistance of *Funestus* vector to synthetic pyrethroids results in the re-introduction of spraying with DDT in the 2nd half of 2000. Also, IRS in Southern Mozambique was introduced just a few months before the implementation of ACT.	IRS activities also date to a couple of decades ago. Unlike KZN, MPUM continues to use synthetic pyrethroids and DDT for spraying. There were no changes in spraying activities before the implementation of ACT in MPUM and cross-border vector control is gradually increasing.
Introduction of SP as first line	1988	1997
Effectiveness of SP at time of change to ACT	12%	93.6%
Choice of ACT	artemether-lumefantrine	artesunate + SP
Time of implementation of ACT	Jan-01	Jan-03
Implementing institution	KZN DOH	Mpumalanga DOH
Year of ACT Evaluation	2002	2003

The selection and timing of implementation of ACT, and implementation processes were different for each study site because of the different existing contextual factors, notably significantly higher levels of resistance to SP and malaria transmission in Kwazulu Natal. Kwazulu Natal changed from SP to artemether-lumefantrine (AL) in January 2001, while Mpumalanga changed from SP to artesunate+SP (AS+SP) in January 2003. There are several similarities that allow for comparisons between different ACT implementation strategies and their impact in terms of cost and health outcomes, despite some differences and constraints outlined below.

3.2: METHODS FOR ECONOMIC EVALUATION OF ACTS IN SOUTH AFRICA

In both Kwazulu Natal and Mpumalanga, for both baseline (2000) and post-intervention (2002/03) periods, costs and health outcomes data were retrospectively collected from a sample of health facilities. A before-and-after study design (i.e. a longitudinal) was used for the evaluation of ACTs in

both Kwazulu Natal and Mpumalanga. The limitations of this study design are discussed in detail in various parts of the thesis in chapters 4, 5 and 7. However, a key limitation of this study design is that in studies aiming to measure the impact of an intervention, it may be difficult to infer that any observed improvements were due to the intervention since there is no control group to ensure that these changes would not take place anyway. The reason for choosing this study design was because the change from SP monotherapy to ACTs was universal in the whole province (for both Kwazulu Natal and Mpumalanga) and as such control study sites could not be considered ethical or feasible. The best approach for such an evaluation, in ideal circumstances, would have been a longitudinal-control impact study where comparisons are made before and after between the intervention sites and the control sites [159]. This evaluation approach was not possible because the universal implementation of ACTs in the sites studied and appropriate control sites could not be found. On the other hand, however, Mpumalanga study sites can be considered as a 'control' site in relation to the evaluation of ACTs in a context of confounding factors, as was the case for Kwazulu Natal.

3.2.1: Methods for conducting Household surveys

A household survey was undertaken with the objective of understanding treatment seeking behaviour for malaria and assessing adherence to treatment among the local populations. In addition, the survey aimed to collect key socio-economic household information. The wider SEACAT evaluation (i.e. the biological modelling and drug utilisation review components) was expected to use the results of the household survey to determine the probable levels of ACT coverage and adherence in each site. A structured household survey questionnaire was designed (by me) and translated into the relevant languages in order for it to be used in all the SEACAT sites (including those that have not been included in this thesis, such as Limpopo province in South Africa, Southern Mozambique and Swaziland). Translation was done from English to the local languages and back into English, by different translators, to ensure accuracy and consistency in translation. In both sites, a group of energetic young men and women were trained (by me) to conduct the household surveys in the local languages. Training of research assistants who conducted the survey was done before the questionnaire was pre-tested in both sites. Appropriate changes to the pre-tested questionnaire were made after the pilot studies. The English version of the questionnaire is attached in Annex 2.

Household surveys were conducted in 437 and 391 households (which comprise of 2509 and 2280 household members) in Kwazulu Natal and Mpumalanga, respectively. In Kwazulu Natal all households in the 7 highest risk sections of Ingwavuma district were surveyed. The basis for the selection of the sections with the highest malaria transmission was to ensure that an adequate number of households 'who had had a malaria case in 4 weeks preceding the survey' would be obtained. With 100% sampling in Kwazulu Natal, researchers moved from one household to another, interviewing and filling in the questionnaire. In Kwazulu Natal, the basis for sampling all households in the 7 highest-risk section was to reflect the communities carrying the highest malaria burden and ensure adequate numbers of households in which there had been a malaria case in the 4 weeks preceding the survey. This was especially important in an area of low intensity malaria transmission. The sampling technique and household selection method used in Mpumalanga was different from those used in Kwazulu Natal. Given the much lower intensity of malaria transmission in Mpumalanga, it was necessary to follow up index cases presenting to sentinel clinics at their homes to identify households with a reasonable probability of having experienced malaria. To address the bias in the Mpumalanga sampling technique control households ("the nearest front door") were also included in the household survey. To ensure consistency between sites, the household survey manager in both sites (Kwazulu Natal and Mpumalanga) was the same (that is, myself) and 2 of the supervisors and two other team members were the same. The household surveys were not designed with the primary objective of comparing Mpumalanga with Kwazulu Natal, and the differences in sampling methods and in intensity of malaria transmission limits the validity of such comparisons.

Analysis of household survey data was done using STATA and other statistical packages. Various groups of people on the SEACAT project were interested in doing different kinds of analyses, so the household survey MS Access databases were shared between researchers. The analyses relating to results that feed into the economic evaluation were primarily undertaken by me.

3.2.2: Economic evaluation perspective

The perspective to be considered for an economic evaluation plays a crucial role in determining the relevant health outcome and costs to be measured, and how they should be measured and valued. From a welfare point of view, the societal perspective is the broadest and the most recommended [102, 120, 160]. The societal perspective in economic evaluations requires that all costs and health

outcomes that flow from an intervention are comprehensively measured and valued, regardless of who experiences the outcomes or costs. However, there is consensus that not all economic evaluations need to be undertaken from this perspective. For instance, the 1993 Panel of Cost-effectiveness in Health and Medicine acknowledges that "... CEA done from other perspectives can reasonably omit some outcomes and costs if they are not of interest to the decision maker" [102, p.6]. In the studies presented in this thesis, the provider perspective was considered (in measuring both costs and health outcomes) mainly because the measurement of all potential health outcomes was not feasible and was beyond the scope of these studies. This being the situation, it would not have been appropriate to estimate costs from a societal perspective and health outcomes from a narrower perspective. Some of the health outcomes that would have been difficult to measure within the timeframes of the economic evaluation include: the potential long-term benefits of ACTs with regard to reducing transmission, reduction of progression to severe malaria and hence death, enhancing the therapeutic useful life of antimalarials, among others. Moreover, findings of the household surveys showed that the direct costs incurred by patients/households are very minimal, and that a small proportion (only 7% in Kwazulu Natal) of the people were employed[7] (SEACAT evaluation, Household survey results). A societal perspective would require that the time of the unemployed patients and the unpaid caregivers be valued at their 'opportunity cost', and this would have been extremely challenging given the equity issues that arise from valuing such indirect costs. Patient direct costs were minimal because, in South Africa, malaria is a notifiable disease, and as such malaria treatment services at all levels of care, in the public sector, are free of charge. One of the findings of the household survey conducted in Kwazulu Natal showed that 97% of the 235 people who had a recent (2 weeks recall) malaria episode had spent nothing on treatment seeking (i.e. on consultation, antimalarials, diagnosis, and transport for patient and caregiver to and from the facilities). A finding of the household surveys conducted in both Kwazulu Natal and Mpumalanga is that about 95% of households first sought care from a public sector health facility if they had symptoms for malaria. Analyses of these household surveys also showed most people (about 90%) walked to a health facility to seek medical care when sick.

[7] There are challenges around estimating indirect costs (time lost from being sick) of people who are unemployed. Under normal circumstances, their 'lost productivity' would be estimated on the basis of their market wage rates.

3.2.3: Facility Sampling Techniques

In Kwazulu Natal malaria cases are restricted to the 2 northern districts. In Kwazulu Natal, data were collected from one district hospital (Manguzi hospital) and 9 fixed clinics in Manguzi sub-district. Manguzi area is located in Ingwavuma district in the northern part of Kwazulu Natal province and borders on southern Mozambique. Manguzi sub-district was purposively sampled because it had the highest number of malaria cases in Kwazulu Natal in 1998-9. Within Manguzi sub-district, there are 9 fixed clinics and 1 district hospital and all of them were included in the study. The total number of facilities studied makes up 100% and 50% of the total number of health facilities in Manguzi sub-district and Ingwavuma district, respectively.

Malaria transmission intensity in Mpumalanga is very low and cases occur throughout the eastern lowveld region of this province. In Mpumalanga, data were collected from two district hospitals (Shongwe and Tonga) and 32 clinics in two sub-districts. In Mpumalanga, the area with the highest malaria prevalence is Tonga district. All the health facilities in Tonga district were included in the study. Tonga district has 15 fixed clinics and 1 district hospital, but the district hospital was fairly new at the time of baseline data collection and hence did not have adequate information to feed into a cost-effectiveness study. For this reason, Shongwe district, which has the second highest prevalence levels, was purposively sampled to be included in the study. Shongwe district has 17 clinics and 1 district hospital (which is also the referral hospital for Tonga hospital), which were all included in the study.

In both Kwazulu Natal and Mpumalanga, clinics studied are satellite clinics for the district hospitals studied. Since records for all satellite clinics are centrally kept at the district hospitals, it was easy to obtain relevant data for all clinics from these hospitals. However, for each sub-district studied, a sample of clinics was physically visited in order to collect some of the information that was not available at the hospital level (such as, the size of the health facility and the quantities of antimalarials consumed at each clinic). Details of how many facilities were studied and how they were sampled are discussed in the individual chapters on each study site.

3.2.4: Calculating Costs in Kwazulu Natal and Mpumalanga

3.2.4.1: Costing period and procedures

To maintain consistency with what most costing guidelines recommend, a 1-year costing period was considered. Baseline data were collected for the year 2000 for both study sites. The basis for the choice of year for baseline was (a) it as the most recent year before the implementation of the interventions in Kwazulu Natal; and (b) it represented the most accurate picture of the consistent pattern of the increasing numbers of malaria cases since 1995. Without a change in treatment policy, the number of patients presenting at healthcare facilities would be expected to continue to increase given the increase in resistance leading to higher treatment failure (recrudescence) rates. As the population is non-immune, these would be expected to become symptomatic and require re-treatment (usually within 6 weeks), further increasing the malaria case load. In addition, the increased gametocyte carriage rates following SP would increase the malaria transmission and thus the rates of new infections in the community. Therefore, the increase in malaria cases up to the year 2000 represented an increasing trend, and cases would certainly have continued to rise in the absence of the described interventions (Delphi Survey). This means that the improvements in health outcomes based on the figures of the year 2000 are an under-estimate of the actual impact of the interventions in Kwazulu Natal. Post-intervention data were collected for the year 2002 and 2003 for Kwazulu Natal and Mpumalanga respectively. In both Kwazulu Natal and Mpumalanga a full costing was undertaken using the ingredients and step-down approaches, for both baseline and post-intervention periods. The clinics in the study sites provide only outpatient services (for all diseases including malaria), and hence refer severe cases of malaria to hospitals for further and/or second line treatment. The ingredients approach was used for the analysis of costs of malaria services at clinic level. On the other hand, hospitals provide both outpatient and inpatient services. Costing at the hospital level employed both ingredients and step-down approaches. First, the step-down approach was used to split costs between outpatient and inpatient services. Thereafter, all resources used in the provision of malaria services (for outpatient and inpatient separately) were costed. Although the focus of the analysis is to evaluate the cost-effectiveness of antimalarial drugs for uncomplicated malaria (i.e. first line therapy), costing of malaria services at inpatient level (i.e. second line therapy) was undertaken. It was necessary to analyse costs relating to hospital admission and second line treatment because

failure of the first line drug may result in progression from uncomplicated to complicated (severe) malaria, hence needing hospitalisation. Moreover, policy on malaria admissions might be influenced by health workers' opinions on effectiveness of first line treatment, as found to be the case in Mpumalanga.

All cost data were converted to 2002 South African Rand using CPIX indices published by Statistics South Africa. All cost data were converted to 2002 US$ at the annual average exchange rate of US $1 = ZAR 10.5.

3.2.4.2: Costs item considered

A full costing requires that both capital and recurrent costs are calculated. Capital costs included replacement costs of buildings, vehicles, furniture and equipment.

Cost of antimalarials and diagnostics were measured. Recurrent cost items included personnel, administration, antimalarials, medical consumables, malaria tests, maintenance, transport, utilities (telephone, water and electricity), other recurrent costs and hotel costs (food provision and laundry).

3.2.4.3: Valuation of Cost items

Cost items were categorised as follows: (1) Costs of antimalarials, (2) diagnostic tests, (3) Other recurrent costs, and (4) Capital costs

Antimalarials

Costs of antimalarials were calculated based on information from health facility records on prices and quantities of antimalarials consumed (dispensed plus wastage) for the given year of analysis. For any given study site, the total cost of antimalarials includes the costs of all antimalarials used for first line in the year of interest. For example, although official first line treatment policy in Kwazulu Natal was SP (monotherapy), the finding in our study sites was that actual practice was frequently the use of SP and CQ in combination. In addition, due to the high failure rates of SP in Kwazulu Natal, oral Quinine was sometimes used to treat outpatient malaria cases. In such cases, the total costs of antimalarials included the costs of SP, CQ and Quinine based in the amounts used and their prices. For the study

sites in Mpumalanga, the cost of antimalarials mainly includes the cost of SP (which was the official first line drug and was the drug actually used to treat uncomplicated malaria). Information on types of drugs used, quantities and prices of each drug used were obtained from the stock cards and other records at the hospital pharmacies. All satellite clinics receive their pharmaceuticals from the hospitals to which they are attached. Information on quantities of antimalarials consumed at clinics were directly obtained from the stock cards at the clinics.

Table 3.2: Methods and data sources for costing antimalarials

Parameter	Source	Means of calculation / quantification
Quantity of antimalarials consumed at **Clinic level**	Hospital pharmacy provided quantities of each drug supplied to each clinic	From the sample of clinics visited, quantities of antimalarials dispensed were obtained from the stock cards. Based on the proportion of antimalarials used in relation to quantities supplied, quantities dispensed at the rest of the clinics were calculated.
Quantity of antimalarials consumed at **Hospital level**	Hospital pharmacy records / stock cards	Antimalarials used for treating outpatients are different from those used for treating inpatients. Cost for each category of antimalarials was calculated separately, and did not require allocating between outpatient and inpatient.
Cost of antimalarials	Prices paid by hospital for each antimalarial obtained from the Hospital pharmacies.	Price of drug multiplied by quantity consumed.

Diagnostics (RDTs and Microscopy)

In South Africa, treatment of malaria is initiated on the basis of a positive diagnostic test. Rapid diagnostic tests (RDTs) are commonly used at outpatient departments (clinics and hospital outpatients). Each hospital has an onsite laboratory equipped with a microscope. Microscopy in malaria diagnosis is usually used when there is a need to confirm the results of a rapid diagnostic test (at outpatient level) and for malaria patients admitted in hospital. At clinic and hospital outpatient levels, the cost of malaria diagnostics was calculated as the number of RDTs used multiplied by the unit price. Cost of microscopy services was based on the estimation (as provided by the head laboratory technician) of usage of reagents, other laboratory consumables and staff time spent on malaria tests and the market prices of each of these items. In South Africa, laboratory services are centralised and hence all staff are paid and reagents are purchased by the national regulating body (not by the health facility where the laboratory is situated). Total costs of malaria diagnostics therefore

include costs of RDTs and of microscopy. Data on number of RDTs used at health facilities was sometimes difficult to obtain due to poor record keeping, and even when they were available they sometimes had gaps. Information on quantities of RDTs used were obtained from the clinics and hospital records, while information on number and estimated costs of microscopy tests were obtained through laboratory reports and interviews with hospital laboratory technicians.

Table 3.3: Methods and data sources for costing malaria diagnosis

Parameter	Source	Means of calculation / quantification
Quantity of RDTs used **Clinic level**	Hospital records	Records included total number of malaria tests done by each clinic (including those that were negative and those that were positive).
Quantity of RDTs used and number of microscopy tests done **Hospital level**	Hospital records Laboratory at hospital	Number of RDT tests done at hospital OPD. Number of malaria smear tests done at lab.
Cost of diagnosis	RDT prices obtained from Hospital pharmacy Price of microscopy obtained from the laboratory.	Price of test multiplied by number of tests done

Other Recurrent cost items

Recurrent costs (for both baseline and post-intervention periods) were calculated on the basis of annual health facility expenditure on recurrent items. Recurrent cost items include personnel-related expenses, administration, facility maintenance, transport, medical consumables and supplies, utilities (water, telephone and electricity), minor equipment, other recurrent expenses, food provision and laundry services (where applicable). Summaries of annual expenditure reports were obtained from the Finance departments of the hospitals studied. The hospitals normally have their records of budgets and expenses, as well as those of the satellite clinics attached to them. Hospital financial reports were detailed enough to provide information on expenditure on each recurrent item. Reports were reviewed and all expenditure items were categorised in one of the above recurrent categories. Interviews were also held with relevant hospital staff to establish whether some of the items were subsidised or donated. There were no subsidised or donated items. Since antimalarials and diagnostics were costed separately, drugs and diagnostic tests were excluded from health facility expenditure in the calculation of 'other recurrent costs' to avoid double counting.

Table 3.4: Methods and data sources for costing 'other recurrent costs'

Parameter	Source	Means of calculation / quantification
Recurrent expenditure **Clinic level**	Hospital records, Finance section	In KZN detailed annual expenditure information for each clinic was readily available. In MPUM, the annual recurrent expenditure was aggregated for all clinics in each district.
Recurrent expenditure **Hospital level**	Hospital records, Finance section	In KZN, detailed annual expenditure for outpatient and inpatient cost centres was readily available. Expenditure available by line item. In MPUM annual expenditure for entire hospital was aggregated. Expenditure available by line item.
Malaria cases and admissions	Hospital records District Health Office	Records for all clinics available at District health office. Malaria cases and admissions obtained from hospitals.
Malaria costs: **Clinic level**		Total annual expenditure minus expenditure on all pharmaceuticals. Allocation factor used: *malaria patients as a percentage of total clinic visits.*
Malaria costs: **Hospital level**		In KZN: (allocation factor) x (annual OPD expenditure, less expenditure on pharmaceuticals)
		In MPUM: used patient-day equivalent to split annual hospital expenditure between outpatient and inpatient departments. Then used allocation factor to calculate costs related to malaria treatment, for outpatients and inpatients.

NOTES:
1. "patient day equivalent" was calculated as malaria inpatient-days + 1/3(malaria outpatient cases).
2. "allocation factor" = malaria outpatient cases (or inpatient-days) as a proportion of total hospital outpatient visits (or inpatient-days)

Capital costs

Capital cost items include buildings, vehicles, furniture and equipment. For buildings, actual physical measurements of health facilities were done, particularly for all the hospitals. In the case of clinics, after finding that all clinics in a given district were more or less the same size and had the same equipment and furniture, a sample of them were physically visited and the buildings were measured. In Kwazulu Natal, 3 out of 9 clinics were measured. The average size of the 3 clinics was used for the remaining 6 clinics. In Mpumalanga, 4 and 5 out of 15 and 17 clinics were visited and measured in Tonga and Shongwe districts respectively. The replacement costs (per square metre) of health facility buildings were obtained from CSIR Building and Construction Technology (based in Pretoria, South Africa). Total replacement value of buildings was calculated as cost per square metre multiplied by number of square metres of the health facility. The annual replacement costs of buildings were calculated as total replacement costs divided by the annualisation factor (of 5% over 30 years). For equipment, furniture and vehicles, inventories were obtained from the health facilities studied. In situations where these were not adequate, physical counts of facility equipment, furniture and vehicles were done. Details of the type and make of these items were obtained. The replacement

costs of each of the furniture and equipment items were obtained from official suppliers of medical equipment in South Africa. Similarly, the replacement cost for vehicles were obtained from several car dealers in South Africa, and an average was obtained. Annual replacement costs for furniture, equipment and vehicles were calculated based on their replacement value at 2002 market prices and annualised at 5% over their estimated useful life. The recommended useful life of capital items considered were buildings – 30 years, vehicles – 10 years, furniture and equipment - 5 years [108]. The 5% annualisation rate was chosen on the basis of recommendations of 3%-5% by most economic evaluation textbooks [32-34, 99].

Table 3.5: Methods and data sources for costing capital costs

Parameter	Source	Means of calculation / quantification
Size of health facility **Clinic level**	Physically measured	A sample of health facilities visited and measured in metres. The average size from the visited clinics was used for the remaining clinics that were not physically measured.
Size of Health facility **Hospital level**	Measured based on hospital plans. In some instances, physical measurement of some of the buildings.	All hospitals were physically visited.
Cost of Buildings		Cost per sq. metre for clinics and district hospitals obtained from CSIR. Total replacement cost calculated, and annualised at 5% over 30 years.
Cost of Furniture and Equipment	Health facility inventories and physical counts in some instances	For clinics, average for the visited clinics used for the remaining clinics not physically visited. For hospitals, all inventories considered. Cost of each item obtained from relevant sources. Replacement costs calculated and annualised at 5% over a 5-year period.
Cost of Vehicles	Transport department of the hospitals. Clinics do not have vehicles.	Cost per vehicle (for the different make of cars) obtained from various car dealers. Total replacement cost of vehicles calculated and annualised at 5% over a 10-year period.

3.2.4.4: Cost allocation procedures

Costing was done for both malaria outpatient and inpatient services. Costs of diagnostics and antimalarials are specific to the management of malaria cases, hence did not need to be allocated. At clinic level, only outpatient-related costs were applicable. At this level, an allocation factor was

calculated on the basis of *number of malaria cases as a percentage of total annual clinic outpatient cases*. Costs relating to the management of malaria cases at clinic level were calculated as a proportion of total facility expenditure, that is, *annual clinic costs* multiplied by the *allocation factor*. This was done for both annual recurrent and capital costs. The basis for using the allocation method described above is not a detailed analysis of case-mix at the facilities studies. The assumption that 'other recurrent costs' for malaria patients are the same as those of non-malaria patients (i.e. when the above method is used for allocation of costs), is based on the findings during key informant interviews (i.e. with 4 nurses and 2 doctors that treat malaria outpatients) at the clinics and hospitals visited, where the personnel involved in the management of all outpatients (including those suffering from malaria) indicated that patients with uncomplicated malaria went through the same procedures as other outpatients in waiting for treatment and that health personnel spent, on average, 10-15 minutes on each outpatient which was almost the same as their estimated amount of time spent with an uncomplicated case of malaria (approx. 10 minutes). This assumption is not unreasonable considering the type of facilities studied (clinics and district hospitals). Such facilities usually handle reasonably uncomplicated illnesses which do not require specialised and sophisticated input (such as surgery). If this assumption was unreasonable, the implication would be that costs for malaria might be under-estimated (if malaria cases actually require more time than other outpatient cases) or over-estimated (if malaria cases actually require less time compared to other outpatient cases).

At hospital level, the step-down costing approach was employed. First, total hospital cost was allocated to outpatient and inpatient departments. The split of total annual hospital recurrent expenditure between outpatient (OPD) and inpatient departments (IPD) was either done directly (as in the case of Kwazulu Natal where such records were readily available) or using patient-day equivalents (1 inpatient day = 3 outpatient visits), as in the case for Mpumalanga. For district hospitals, such as those studied here, it is estimated that 3 outpatients are equivalent to 1 inpatient-day [161]. Capital costs were split between OPD and IPD on the basis of proportion of space each department occupies. Then, recurrent and capital costs were allocated to management of malaria patients (outpatient and inpatient). For outpatient services, the allocation factor was calculated as the number of malaria outpatients as a percentage of total annual hospital outpatient visits. Annual costs of malaria outpatient services were thus calculated as *annual OPD recurrent and capital expenditure* multiplied by *the allocation factor*. Similarly, annual costs of malaria inpatient services were calculated

as allocation factor (malaria inpatient days as a percentage of total hospital inpatient days) multiplied by annual inpatient recurrent and capital costs.

3.2.5: Calculating costs of implementing new treatment policy

Implementation of AL in Kwazulu Natal

A description of the process of introducing AL as first line treatment is presented in chapter 4 (section 4.2.2.1). Costs incurred for conducting policy meetings and telephone conferences, printing new treatment guidelines and for re-training health workers were obtained through key informant interviews. These costs were incurred by the Kwazulu Natal Department of Health, the Kwazulu Natal Malaria Control Program and the Malaria Advisory Group. Expenditure data for these items was obtained for the year 2000/2001, inflated to ZAR 2002 prices and converted to 2002 US $ using an exchange rate of US$ 1 = ZAR 10.5.

Implementation of AS+SP in Mpumalanga

As in Kwazulu Natal, the process of changing to AS+SP was the responsibility of Mpumalanga Department of Health and included stakeholder negotiations and consensus building, particularly around the choice of ACT, and the procedures for implementing this change. Mpumalanga opted to combine SP with artesunate because, unlike in Kwazulu Natal, SP was still highly effective (95% cure rate) in Mpumalanga at the time of policy change [162].

In both study sites, there is a well-established and effective Malaria Control Program (MCP) (within the Department of Health) whose role is to undertake malaria control activities (particularly vector control though IRS and guide treatment policy). The cost of the implementation process excludes the costs of the drugs as these have been captured in the analysis of treatment costs.

3.2.6: Calculating cost of Insecticide residual spraying in Kwazulu Natal

At baseline Deltamethrin was used to spray all structures. During the intervention year, Kwazulu Natal sprayed reintroduced DDT (for the indoor residual spraying of only traditional style structures which constituted about 40% of total structures) while Deltamethrin continued to be sprayed on western

style structures (in the remaining 60%). The cost of spraying with Deltamethrin in 1999 was estimated as the cost per person covered of R14.6 [163] multiplied by the population of Ingwavuma district in 1999. For the intervention period, the cost of "*spraying with DDT and Deltamethrin*" was estimated as the average cost per person covered of R15.6 multiplied by the Ingwavuma population in 2000. This cost was extrapolated from Goodman and other's costing of IRS which included costs of personnel, insecticide, other supplies, vehicle operation and maintenance, storeroom as well as capital costs [163]. In relation to cost of spraying with DDT it was assumed that the only costs that would change would be the cost of insecticide, hence adjustments were made to Goodman's estimate by changing the cost of insecticide. The estimated cost was inflated to 2000 prices. The evaluation of costs and benefits of IRS were done separately first and then combined with those for ACTs in Kwazulu Natal, but not in Mpumalanga.

In Mpumalanga, vector control through IRS has been in place since the late 1950s. Unlike Kwazulu Natal, Mpumalanga did not have any changes in their usual IRS strategies (e.g. change of insecticide) for vector control. The results for Mpumalanga as a study site will be helpful for interpreting the Kwazulu Natal findings, particularly around comparing the impact of ACT with and without changes in vector control methods. The findings on cost-effectiveness of ACTs from both study sites, however, cannot be generalised to other African settings because the concurrent effective vector control measures and relatively strong health care infrastructure in the 2 study sites are often lacking in other African settings.

3.2.7: Calculating effectiveness of ACTs

Effectiveness of ACTs has been evaluated in terms of intermediate health outcome mainly including number of malaria cases, malaria cases cured, malaria admissions and deaths. Health outcomes data were collected retrospectively for baseline (2000) and post-intervention periods (2002/3) from health facility records in both Kwazulu Natal and Mpumalanga from health facility records. Malaria cases successfully cured were calculated as the number of malaria cases multiplied by the cure rates (as obtained from the in vivo therapeutic efficacy studies) of each antimalarial. The use of 'number of malaria cases cured' as an outcome measure may have limitations. As the number of cases cured is based on cure rates achieved in trial settings, they may be an overestimate, given that the effectiveness of a particular drug may be lower when used in field settings (e.g. due to deterioration of

drugs not stored in appropriate conditions and non-compliance by patients). However the high levels of self-reported adherence in the household survey suggest that it was reasonable to assume that similar cure rates could be achieved in non-study settings. A comparison of supervised and non-supervised artemether-lumefantrine treatment showed no difference in cure rates [164]. It is important to add that no explicit assumptions on the expected useful therapeutic life of ACTs have been made and/or taken into consideration in the analyses. As such, no future projections of the effectiveness of ACTs were included.

In Kwazulu Natal, where the effect of changes in vector control and the introduction of IRS in Mozambique are believed to have substantially contributed to the reduction in malaria cases, the calculation of intermediate health outcomes involved apportioning some of the decline in malaria cases, admissions and deaths to the introduction of AL as first line treatment of uncomplicated malaria. Delphi estimates of the percentage contribution of AL were used. The methods of obtaining the Delphi estimates are described in chapter 4. In Mpumalanga, where there were no changes in the insecticide and no major confounding factors identified, the changes in malaria-related outcomes (e.g. decline in malaria cases, deaths, etc) can be argued to be a direct result of the change in treatment policy. Given the geography of the study areas (separated by Mozambique and Swaziland), the vector control activities in Kwazulu Natal should not have any impact on malaria prevalence in Mpumalanga. However, given Mpumalanga's proximity to some parts of southern Mozambique, it is possible that the introduction of IRS activities in southern Mozambique had an influence in malaria transmission in the neighbouring areas in Mpumalanga. The impact of IRS in Mozambique on malaria transmission in Mpumalanga, by 2003, is not expected to have been substantial (Aaron Mabuza, Mpumalanga Malaria Control Programme Manager, *Personal Communication*).

3.2.8: Evaluating cost-effectiveness

Data on costs and health outcomes were combined to calculate cost-effectiveness. First, ACTs were evaluated over a short timeframe, taking into consideration data 1-2 years from the time ACTs were implemented. No future costs and effectiveness of ACTs (i.e. projections into the long term) were estimated or included in the analysis. Unit costs associated with the use of the different antimalarials have been calculated and compared. Incremental cost-effectiveness was calculated as change in

costs (difference between baseline and post-intervention costs) divided by change in health outcomes. Also, the relative cost-effectiveness of ACTs in relation to SP was calculated using a simple decision tree model to capture the aggregated impact of ACTs on malaria case management in the public sector.

3.2.9: Decision Tree Analysis

A simple decision tree has been used to evaluate and compare the cost-effectiveness of ACTs in Kwazulu Natal (comparing SP monotherapy and artemether-lumefantrine) and Mpumalanga (comparing SP monotherapy and artesunate + SP). The decision tree combines the costs and health outcomes associated with case management at both outpatient and inpatient levels. The decision tree takes into consideration the probabilities of failing treatment with each first line antimalarial as well as the probability of being hospitalised after failing treatment. The probabilities used in the decision tree are based treatment seeking and case management of uncomplicated and severe malaria in the contexts of Kwazulu Natal and Mpumalanga, respectively.

The decision trees consider 2 branches at the root node, each branch representing the first line treatment options being evaluated (SP monotherapy vs. ACTs). At each of the treatment nodes there are 2 possible outcomes; either a patient is cured or fails treatment. For a patient who fails treatment, the next possible outcome is that they seek treatment and receive first line treatment again (if they are diagnosed to have uncomplicated malaria) or they will seek treatment and be hospitalised where they received second line treatment – Quinine (if they are diagnosed as having severe malaria). The reason why receiving first line treatment for the second time is considered a possibility after failing the first treatment is because patients may present with malaria at health facilities a few weeks after their last treatment and it is difficult for health workers to tell whether it is a case of failed treatment (recrudescence) or a re-infection. In the unlikely event of a patient who fails treatment with a first line antimalarial twice but does not seek care at a hospital, they are assumed to have a 50% chance to cure naturally or to die from malaria. This 50-50 chance is arbitrarily assumed because there is no research evidence that documents the probability of a non-immune patient surviving repeatedly resistant malaria without treatment. With the hospitalisation option, the outcomes considered are that either the patient is cured or they die.

Figure 3.2: Simple decision tree used in the cost-effectiveness evaluation of ACTs

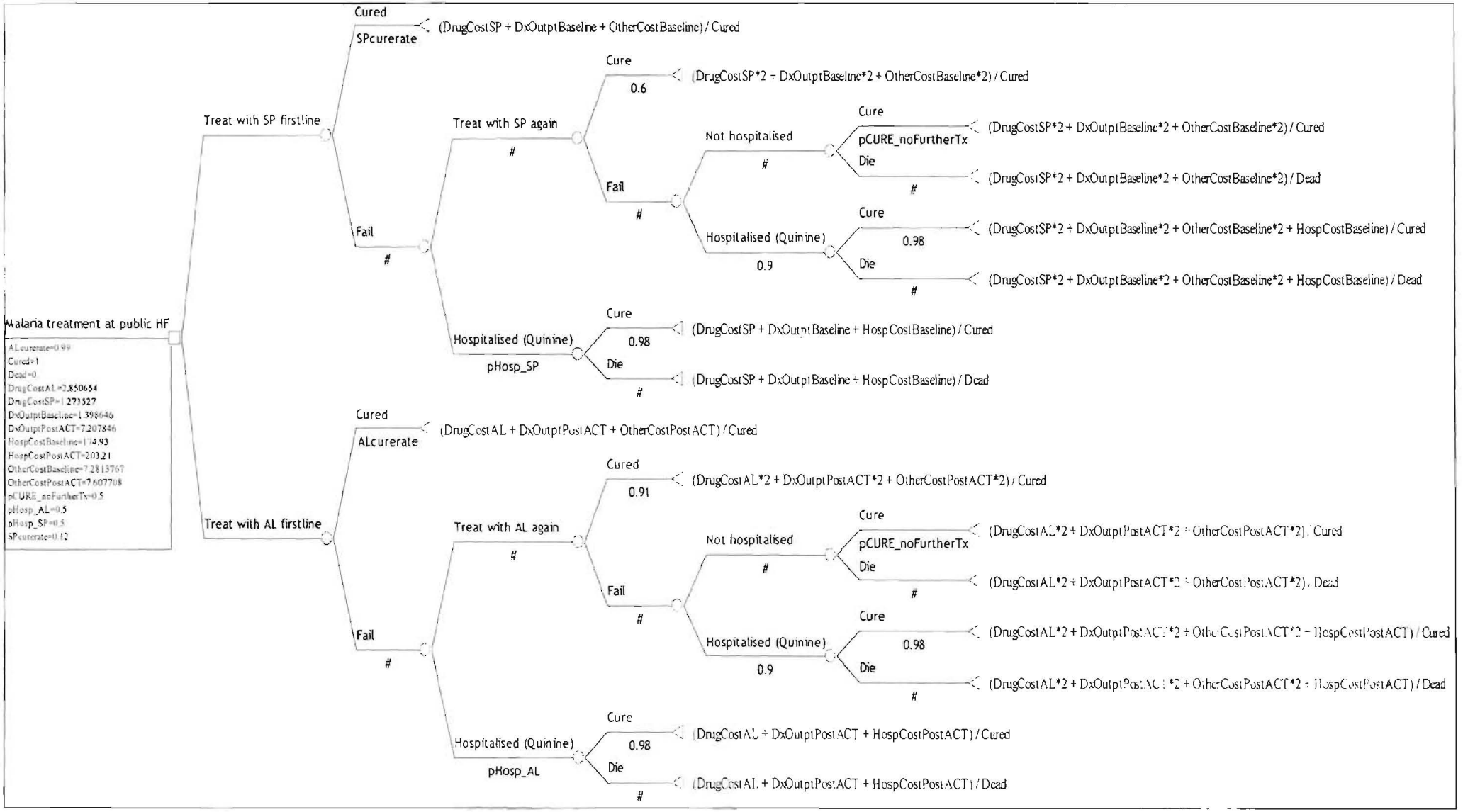


Table 3.6: Definition of variables used in the decision tree

Variable	Definition	Value for Kwazulu Natal	Value for Mpumalanga	Source of value
ALcurerate	cure rate[8] for artemether-lumefantrine (AL)	0.99		SEACAT study findings
ASPcurerate	cure rate for artesunate + SP		0.99	
SPcurerate	cure rate for SP	0.12	0.95	Study sites undertaken in Kwazulu Natal and Mpumalanga.
Cured	Outcome of treatment being CURED	1	1	Dummy values
Dead / Die	Outcome of treatment being DEAD	0	0	
DrugCostAL	cost of artemether-lumefantrine per malaria outpatient	$2.85		Data collected during this study from the sampled health facilitie in the study sites previously described, for both Kwazulu Na and Mpumalanga. Prices of SP are different for Kwazulu Natal and Mpumalanga because the 2 provinces procure drugs separately and from different sources.
DrugCostASP	cost of artesunate+SP per malaria outpatient		$1.69	
DrugCostSP	cost of SP per malaria outpatient	$1.27	$2.41	
DxOutptBaseline	cost of diagnosis for malaria outpatients at baseline	$1.40	$2.27	
DxOutptPostACT	cost of diagnosis for malaria outpatients after ACT implementation	$7.21	$5.92	
HospCostBaseline	cost of treating one malaria inpatient (including diagnosis, drugs and other costs) at baseline	$174.93	$399.91	
HospCostPostACT	cost of treating one malaria inpatient (including diagnosis, drugs and other costs) after ACT implementation	$203.21	$155.25	
OtherCostBaseline	Other costs related with treatment of malaria outpatients at baseline, excluding cost of antimalarials and diagnosis	$7.28	$5.62	
OtherCostPostACT	Other costs related with treatment of malaria outpatients after ACT implementation, excluding cost of antimalarials and diagnosis. Such costs include recurrent and capital costs of health facilities.	$7.61	$3.56	
pCURE_noFurtherTx	probability that a patient who has failed first line treatment twice and has not sought further treatment is cured.	0.5	0.5	Because there is no empirical literature on this, the value here has been assumed.
pHosp_AL	probability that a patient who has failed to get cured with artemether-lumefantrine (first time) will seek care at a hospital and will be hospitalised to get second line treatment.	0.5		Conservatively assumed values based on limited available hospital and in vivo study data. Since it difficult to estimate the degree of severity of disease associated with treatment failure (for each drug). Although there are higher chances of treatment failure with SP, but it is difficult to predict progression to severe disease resulting from this treatment failure. Sensitivity analyses of these probabilities have been undertaken (for values between 0.1 and 0.8).
pHosp_SP	probability that a patient who has failed to get cured with SP (first time) will seek care at a hospital and will be hospitalised to get second line treatment.	0.5	0.5	
pHosp_ASP	probability that a patient who has failed to get cured with artesunate+SP (first time) will seek care at a hospital and will be hospitalised to get second line treatment.		0.5	

NOTE: Example of drug used in decision tree (Figure 3.2) is AL, but Table 3.6 gives values for both antimalarials (AL and ASP)

[8] Cure rate / and Therapeutic efficacy are defined as An Adequate Clinical and Parasitological Response over 42 days of follow up (WHO Guidelines for the treatment of malaria 2006).

3.2.10: Sensitivity analysis

One-way and multi-way sensitivity analyses were conducted to explore the impact of changes in estimates for variables where data were inconsistent or not readily available. The variables mainly include: annualisation rate for capital costs, number of days for hospitalisation of malaria patients, percentage contribution of the ACT to the decline in malaria incidence (in the case of Kwazulu Natal), number of malaria cases in the absence of malaria control interventions, and price of SP in Kwazulu Natal and Mpumalanga. Also, sensitivity analyses were done for the variables in the decision tree presented in Table 3.6.

3.3: CONCLUSIONS

Despite the contextual differences between the study sites, there are several similarities that allow comparison of findings between the sites. Firstly, both sites are low malaria transmission areas. Secondly, there have been effective vector control measures, mainly through IRS, for an extended period of time in both sites. Thirdly, both sites were using the same antimalarial (SP) for first line treatment at baseline. Lastly, both sites are in the same country, hence have similar public health care infrastructure and there is no need for purchasing power parity conversions as far as costs are concerned. The differences in the study sites help us to evaluate various issues. Firstly, the role and impact of change in insecticide for IRS in Kwazulu Natal can be evaluated. Secondly, some lessons can be drawn from the comparison of two different types of ACTs (AL and AS+SP).

The methods used in measuring and valuing costs were the same for both study sites, for both baseline and post-intervention evaluations. The health facilities included in studies at baseline were the same as those included on the post-intervention analysis, for both Kwazulu Natal and Mpumalanga study sites. The methods used for measuring health outcomes were the same for both sites, with the exception of the need to apportion impact to various interventions in Kwazulu Natal. The Delphi technique was employed to estimate the proportion each of the 3 interventions contributed to the reduction in malaria morbidity and mortality in Kwazulu Natal.

The uniqueness of interventions being evaluated poses methodological challenges. To calculate the cost-effectiveness of ACTs, there was need to deal with these methodological challenges. Specifically, four types of analyses were undertaken in order to address some of the challenges, namely:

- Using the Delphi technique to obtain information on estimates of each intervention's contribution to the decline in malaria morbidity and mortality in Kwazulu Natal, and also to obtain information on possible malaria morbidity and mortality in the absence of change to AL.
- Using a decision tree to undertake an analysis that combines the impact of ACTs on both costs and health outcomes associated with improved management of both uncomplicated and severe malaria.
- Undertaking extensive multiway sensitivity analyses on variables whose values are uncertain.
- Comparisons between the two study sites to assess the robustness of the Delphi estimates of the role of IRS.

Further details on the methods used for and the findings of these analyses are presented separately in chapters 4-6.

4. ECONOMIC EVALUATION OF MALARIA CONTROL INTERVENTIONS IN KWAZULU NATAL

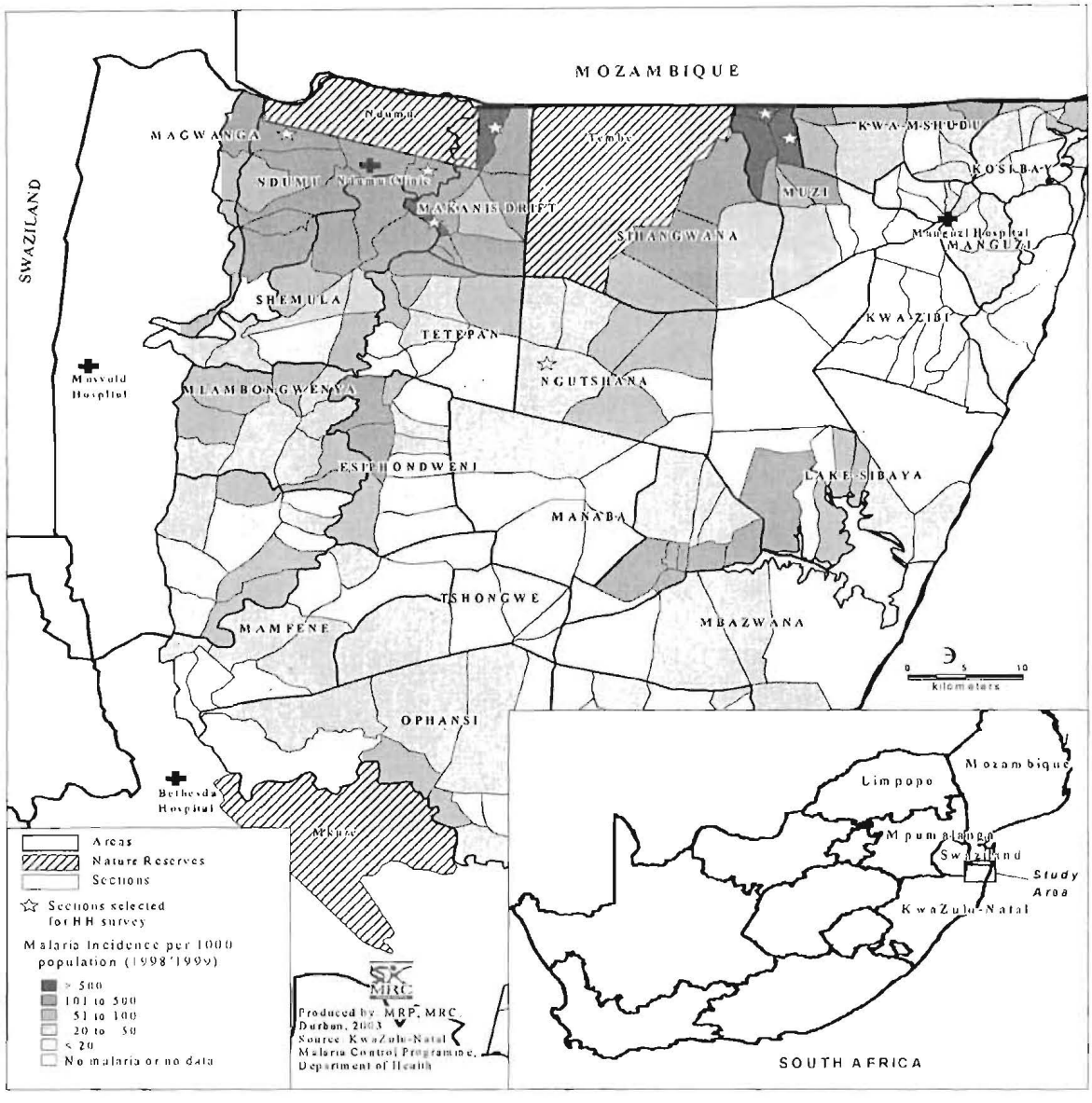
4.1: INTRODUCTION

Malaria transmission in South Africa has been restricted to the north-eastern areas bordering on Mozambique and Zimbabwe (Figure 4.1) through the effective vector control with widespread indoor residual spraying (IRS) and the provision of prompt, effective treatment since 1958. The intensity of malaria transmission in Kwazulu Natal is low, with an annual Entomological Inoculation Rate (EIR) of less than 1 (i.e. the probability of an infectious mosquito bite is less than once per person per year). Transmission is seasonal, mainly occurring between January and May (Figure 4.2), and *Plasmodium falciparum* accounts for the majority of malaria infections.

The study site, Ingwavuma district, is the northern most district of Kwazulu Natal (bordering Mozambique) and had the highest malaria incidence in the country, with 80 – 242 cases per 1000 population recorded in sub-districts in Ingwavuma district in 2000. Ingwavuma district is largely rural with a population of 182,342 people in 2000. Ingwavuma district has two district hospitals, 23 clinics and several mobile clinics. The results of the household survey undertaken in 2001 (as part of the SEACAT evaluation) showed that the socio-economic indicators in this area are characterised by high levels of unemployment, low levels of educational attainment, low levels of income and lack of proper basic services, such as clean water, electricity and proper sanitation (see section 4.3.1).

Health services in Kwazulu Natal are fairly adequate, with primary health care services within 10km from 77.4% of households [165]. Health services, including the treatment of malaria, are offered at 3 levels, namely: clinics and mobile clinics, district hospitals and regional hospitals. Within Ingwavuma district, Manguzi sub-district, comprising of 9 fixed clinics and 1 district hospital, was purposively sampled because it had the highest malaria incidence in 1998-1999 (Figure 4.1).

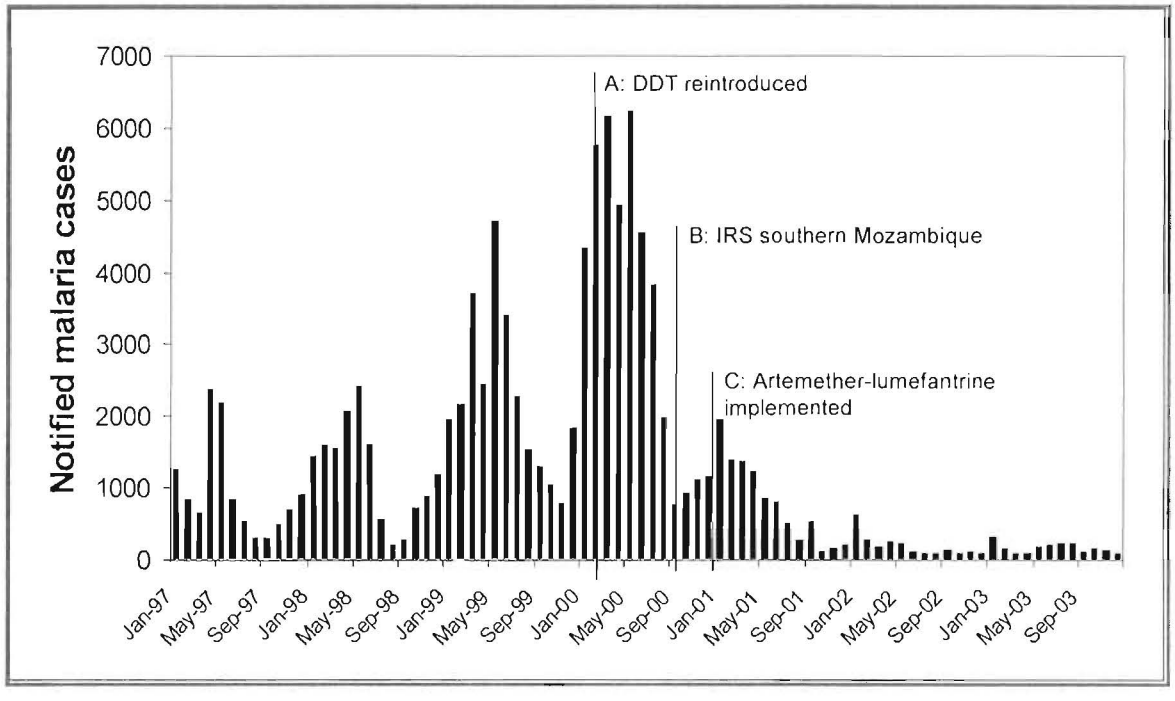
Figure 4.1: A detailed map of malaria incidence (1998-1999) and sites selected for household survey in Kwazulu-Natal.



In Kwazulu Natal province, sulphadoxine-pyrimethamine (SP) replaced chloroquine as first line treatment of uncomplicated malaria in 1988. Notifications of confirmed malaria cases increased dramatically from 1996 onwards, reaching epidemic levels in 1999 - 2000. Following 12 years of SP use in Kwazulu Natal, the therapeutic efficacy of SP (based on an *in vivo* study with 42 day follow-up) was only 12% by 2000 [166]. The rapid development of resistance to SP (resulting in high levels of treatment failures [88%] and a large pool of gametocytes), increased vector resistance to pyrethroid insecticides and the reinvasion of the highly anthropophilic *Anopheles funestus* vector are considered to be the most important contributors to the 1999-2000 malaria epidemic in Kwazulu Natal [167].

Following the malaria epidemic in Kwazulu Natal in 1999 and 2000, several malaria control initiatives were put in place which led to a dramatic decline in malaria incidence in Kwazulu Natal since 2000 (see Figure 4.2). Firstly, the Kwazulu Natal Department of Health addressed vector resistance by re-introducing DDT to replace pyrethroids for indoor residual spraying of traditional (but not western style) homesteads in March 2000 as pyrethroid resistance had been documented in Kwazulu Natal [167]. DDT is not suitable for indoor residual spraying of western style structures. Secondly, a regional collaboration implemented a community-based IRS programme in neighbouring southern Mozambique in October 2000. Lastly, in response to high levels of SP treatment failure, first line treatment of uncomplicated malaria was changed to an artemisinin-based combination therapy (ACT), artemether-lumefantrine (AL), in January 2001. Quinine remains the recommended treatment for severe malaria, and uncomplicated malaria in pregnant women and infants under one year of age.

Figure 4.2: Number of notified malaria cases in Kwazulu-Natal by month in relation to timing of significant malaria control interventions.



Source: South African National Department of Health Notification Data

Figure 4.2 illustrates the seasonality of malaria in Kwazulu Natal, with the peaks being around May and lowest incidence being around September every year. The synergistic impact of strengthening vector

control (through re-introducing DDT IRS of traditional style homesteads together with the introduction of IRS in Mozambique) and the change in the first line treatment policy to artemether-lumefantrine, is shown by the dramatic reduction in malaria notifications in the subsequent years (2001 and 2003).

This chapter presents and discusses the findings of an economic evaluation study initiated to establish whether or not the malaria control interventions – particularly the introduction of ACT (artemether-lumefantrine) as first line treatment in the public sector - in Kwazulu Natal, are cost-effective. Although cost-effectiveness analyses are essentially undertaken to guide decision making on resource allocation, this particular study was undertaken after the policy changes were already in place. The purpose for this evaluation was to determine the cost-effectiveness of artemether-lumefantrine implementation in Kwazulu Natal, within the context of other malaria control initiatives. This would provide information on the appropriateness of the malaria treatment policy change decision in Kwazulu Natal, and may contribute to policy decision-making in other provinces of South Africa and in other African countries faced with the issue of declining effectiveness of chloroquine and / or sulphadoxine-pyrimethamine. The results presented in this chapter evaluate the costs and cost-effectiveness of artemether-lumefantrine in the Kwazulu Natal context, based on the changes in costs and health outcomes associated with the introduction of artemether-lumefantrine relative to the use of SP. Results of the joint evaluation of both ACTs and effective IRS programs are also presented and discussed in this chapter. On the basis of these results, policy issues related to cost and affordability of ACT in South Africa and other sub-Saharan African countries are discussed.

The rest of this chapter is structured as follows: Section 4.2 describes the methods used that are specific to the evaluation of artemether-lumefantrine and other malaria control interventions in Kwazulu Natal. General economic evaluation methods used to collect and analyse data relating to costs, health outcomes and cost-effectiveness, across all study sites, have been discussed in chapter 3 and are not repeated in this chapter. Section 4.3 presents and discusses the findings of the evaluation in terms of costs, health outcomes and cost-effectiveness of each intervention. In section 4.4, these findings are discussed in a broader context to underscore the key findings of the study, and conclusions and recommendations are presented.

4.2: METHODS

The sources of data used in the economic evaluation for Kwazulu Natal are presented in Table 4.1, obtained for all the health facilities in Manguzi sub-district (i.e. 10 of 23 health facilities in Ingwavuma district).

Two interventions, '*change of treatment policy to artemether-lumefantrine in Kwazulu Natal*' and '*improving the vector control strategy through re-introducing DDT for insecticide residual spraying of traditional structures in Kwazulu Natal*', have been considered in this chapter. The methods used for evaluating these two interventions are discussed in sections 4.2.1 – 4.2.4 below.

Table 4.1: Types and Sources of Data in Kwazulu Natal

Type of data	**Source/method of collection**
At Clinic Level	
Expenditure (recurrent and capital)	Manguzi Hospital, Financial Summary from system
Total PHC headcounts	Clinics records & Manguzi Hospital records
Number of malaria patients	Clinics records & Manguzi Hospital records
No. of staff at each clinic and their activities/duties	Interviews at clinics & Manguzi hospital records
Malaria treatment methods for uncomplicated malaria	Interviews at clinics / Manguzi hospital
Quantities of antimalarial drugs dispensed in year	Stock cards for each antimalarial at clinic
Size of the facility	Physically measured (for the 2 clinics visited)
Equipment & furniture	Inventory at clinics
At Hospital Level	
Expenditure (recurrent and capital)	Financial Management System Reports 2000 obtained from hospital
Total outpatient headcounts	Hospital records
Number of malaria outpatients	Hospital records
Total number of admissions	Hospital records
No. of malaria admissions	Hospital records
Total no. of inpatient days	Hospital records
No. of malaria inpatient days	Hospital records
No. of malaria deaths	Hospital records
No. of staff & their activities/duties	Hospital records & interviews with relevant staff.
Malaria treatment methods for uncomplicated & complicated malaria	Interviews with relevant staff & records.
Quantities & prices of antimalarial drugs dispensed	Hospital pharmacy and KZN drug Depot
Size of the facility	Measured from plan of hospital
Equipment & furniture	Physical counts & inventories

4.2.1: Conducting the Household Survey in Kwazulu Natal

The methods for conducting the household survey in Kwazulu Natal are described in chapter 3 (section 3.2.1).

4.2.2: Calculating Health Outcomes

This chapter is concerned with the evaluation of (a) the change of malaria treatment policy from SP monotherapy to artemether-lumefantrine in the public sector and (b) the integrated approach of malaria control through effective treatment (with artemether-lumefantrine) and improving vector control using IRS (DDT / pyrethroids). Indoor residual spraying in southern Mozambique may have contributed to the decline in malaria cases in Kwazulu Natal. However, IRS in southern Mozambique has not been included in this analysis as it is considered to have had a relatively small impact on malaria cases and admissions in Kwazulu Natal, compared to the two local interventions, and because of lack of access to data on the costs of this intervention at the time of this study. The impact of IRS in Mozambique would include the cross-boundary flows of patients coming over to seek medical care in the neighbouring health facilities in Kwazulu Natal.

The standard guidelines for conducting economic evaluations have an implicit assumption that interventions are implemented in isolation (i.e. no confounding factors) and/or that their impact alone can be accurately quantified [32, 34, 109]. Although the concurrent implementation of effective IRS and antimalarial treatment policy has undoubtedly benefited public health, it precludes precise quantification of the individual impact of each of the 3 interventions (see Figure 4.2). The sequential implementation of 2 key malaria control interventions in Kwazulu Natal in quick succession poses methodological challenges to quantification of the impact of the intervention of interest (i.e. the change in policy to artemether-lumefantrine).

Given this contextual issue, a Delphi survey was conducted in an attempt to reach consensus on the approximate percentage contribution of each intervention to the decline in malaria cases, admissions and deaths. Delphi is a method for obtaining consensus among a diverse group of individuals who are knowledgeable about a specific area of interest. Such consensus development methods aim to establish or develop consensus in situations of uncertainty or lack of evidence about the effectiveness of health care (or other) interventions. The Delphi technique has been used in situations when the measurement of a given phenomenon cannot be achieved through other methods. Delphi, as a forecast technique, is a procedure based on subjective information, which allows the researcher to collect anonymously and separately the opinions of several experts on one specific topic [168, 169]. One of the advantages of the

Delphi technique is that, when used correctly, it quantifies a phenomenon that would have otherwise been impossible to quantify. However, results of Delphi surveys may be invalid. Van Zolingen and Klaassen argue that the value-led nature of feedback and consensus and the instability in responses can compromise the validity and reliability of results, and they indicate that results are influenced by, among other things, the number of experts, their average expertise and the average inter-correlation of their judgement [25]. Other factors that might influence results include: biased selection of experts, the design of the questionnaire and poor analysis of results [170]. In this study, the Delphi technique was used because there were no robust methods to separate the entangled impact of all the malaria interventions in Kwazulu Natal, previously discussed (Figure 4.2).

In this Delphi survey, a group of 10 international malaria experts (Listed in Annex 1) was identified by a senior member of South Africa's Malaria Advisory Group to serve as the panellists on the survey. The number of participants in a Delphi survey largely depends on the number of topics, the fields and the expected response rate, among others. Although an estimate of 15-30 people is considered to be an adequate panel size [171], researchers using the Delphi technique have had panel sizes of between 9 and 305 people [171-174]. These panellists were chosen on the basis of their expertise in the areas of malaria transmission, IRS, malaria case management and their understanding of malaria in settings similar to Kwazulu Natal. In addition, the selection of panellists attempted to balance any possible bias in favour of vector control versus ACT case management and to cater for national and international representation[9]. A questionnaire was designed and later refined to take into consideration comments from a malaria expert and a senior health economist at the University of Cape Town. The ten suggested panellists were approached with a request for their participation in the survey, and all consented. All communication was done electronically, through email, and emails sent to the entire panel were sent as blind copies. In the first round of the survey, the questionnaire was sent electronically to the panellists requesting them to describe the major determinants of improved malaria control in Kwazulu Natal and to provide estimates of the percentage contribution of each intervention. In the second round of the survey, summaries of the first round estimates were provided, together with additional literature suggested by panellists as being relevant, to assist them in revising their first round estimates. The summaries of responses provided did not include the identities of the participating panellists. Nine, eight and seven

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[9] In a Delphi survey, it is recommended that the selection of experts ensures that expertise is both varied and extensive 175. Rowe, G. and G. Wright, *The Delphi technique as a forecasting tool: issues and analysis.* International Journal of Forecasting, 1999. **15**: p. 353-375..

panellists responded in Rounds 1, 2 and 3 respectively, the final seven having responded in all rounds. The median estimates obtained from Round 3 have been used in this analysis and are presented in section 4.3.2.

Health outcomes for the analyses in this chapter have been measured as the number of confirmed malaria cases, admissions and deaths. Health outcome measures were considered for two scenarios. Table 4.2 presents a comparison of these scenarios with a description of the costs and health outcomes for each scenario. For scenario 1, health outcomes include only a proportion (based on estimates from the Delphi survey) of the decline in malaria cases, admissions and deaths (Table 4.7). For scenario 2, health outcomes include the combined percentage contribution of Artemether-lumefantrine and DDT/Deltamethrin IRS in Kwazulu Natal to the decline in malaria cases, admissions and deaths (Table 4.7). Sensitivity analysis for scenario 2 was performed using 100% of the decline in malaria cases, admissions and deaths, assuming that the impact of other factors, such as IRS in Mozambique and climatic changes, were small enough to be excluded from this analysis.

Table 4.2: Description of cost analysis scenarios

	Scenario 1: artemether-lumefantrine intervention		**Scenario 2: artemether-lumefantrine + improved IRS in KZN**	
	Baseline	*Post-intervention*	*Baseline*	*Post-intervention*
Description	Treat with SP 1st line and Quinine 2nd line	Treat with artemether-lumefantrine 1st line and Quinine 2nd line	Treatment as in scenario 1 baseline + spraying KZN with Deltamethrin (100%)	Treatment as in scenario 1 post-intervention + spraying KZN with Deltamethrin (60%) and DDT (40%)
Cost	Baseline Cost per malaria patient x number of malaria cases in Ingwavuma district in 2000	Post-intervention Cost per malaria patient x number of malaria cases in Ingwavuma district in 2002.	Scenario 1 baseline costs + cost of spraying with Deltamethrin (100%) in Ingwavuma district.	Scenario 1 post-intervention costs + cost of spraying with Deltamethrin (60%) and DDT (40%) in Ingwavuma district
Health Outcomes	Number of malaria cases, admissions and deaths in Ingwavuma district in 2000	36% of decline in number of malaria cases and 46% of reduction in malaria admissions in Ingwavuma district in 2002.*	Number of malaria cases, admissions and deaths in Ingwavuma district in 2000	82% of decline in malaria cases and 82% of reduction in malaria admissions **
Sensitivity analysis		25%-50% decline in cases and 35%-60% decline in admissions.*		100% of decline in malaria cases and 100% reduction in malaria admissions in Ingwavuma district

* Percentages are derived from the Delphi estimates of the median contribution of artemether-lumefantrine to changes in malaria health outcomes. The ranges (lower and upper estimates) were used for sensitivity analyses.

** Percentages are derived from the Delphi estimates of the median combined contribution of artemether-lumefantrine and IRS in Kwazulu Natal to reduction in malaria health outcomes. These percentages exclude the estimated effect of IRS in Mozambique and other possible factors (such as climatic changes).

4.2.3: Calculating Costs

Methods for calculating the costs of insecticide residual spraying in Kwazulu Natal are described in chapter 3 (section 3.2.5); hence they are not repeated here.

4.2.3.1: Calculating costs of policy change to artemether-lumefantrine

The process of changing from SP to artemether-lumefantrine in Kwazulu Natal included consensus building among various stakeholders, but actual implementation was mainly the responsibility of the Kwazulu Natal Department of Health (DoH). High levels of resistance in *P. falciparum* to chloroquine, SP and amodiaquine precluded their use in an artemisinin-based combination in Kwazulu-Natal [166, 176] In addition, artemether-lumefantrine was the only ACT available in 2000 with sufficient data to support fast track registration by the Medicines Control Council (MCC), the South African drug regulatory authority.

The costs of the implementation process include the costs of policy meetings, printing new treatment guidelines and costs of re-training health workers. Expenditure data for these items was obtained for the year 2000/2001, inflated to ZAR 2002 prices and converted to 2002 US $ using an exchange rate of US$ 1 = ZAR 10.5. The cost of the new drugs has been included in 'treatment costs' (i.e. the cost of antimalarials consumed in providing malaria treatment at health care facilities) and hence has been excluded from the implementation costs to avoid double counting. However, the cost of expired antimalarials has not been included in implementation costs as it was not possible to obtain information on the quantity of artemether-lumefantrine that expired. Anecdotally however, a fairly substantial amount expired because the massive reduction in malaria cases was not predicted, and also because of the short shelf life of Coartem®.

The DoH Pharmaceutical Services undertook, as part of normal routine work, withdrawal of SP and distribution of artemether-lumefantrine. Monitoring and surveillance of the introduction of the new drug was also conducted as part of normal activities by the Malaria Control Program and health care facilities in collaboration with academic institutions, so there were no additional costs incurred for these activities.

4.2.3.2: Calculating costs for the "artemether-lumefantrine intervention" alone

The general methods used for calculating costs related to treating malaria patients have been described in chapter 3 (section 3.2.3) and will not be repeated here. Health facility costs were allocated to malaria on the basis of the *proportion of malaria patients in relation to total annual number of patients* seen at a given health facility. The actual number of malaria patients for the post-intervention period in Kwazulu Natal reflects the impact of the 3 interventions previously described. In the absence of other interventions, the artemether-lumefantrine intervention alone would have resulted in different health outcomes and hence costs. Estimation of malaria costs relating to the evaluation of the ACT intervention alone included apportioning total health facility expenditure to the management of malaria patients alone. In doing this, an allocation factor (i.e. proportion of malaria outpatient cases to total outpatient cases) was calculated. It is important to note here that in the scenario of evaluating the ACT (artemether-lumefantrine) intervention alone, the "**number of malaria outpatient cases**" (i.e. the cases that would have been achieved in the absence of the other malaria control interventions in Kwazulu Natal) is calculated on the basis of the Delphi estimates of the contribution of the ACT intervention (36%) to the decline in number of malaria cases observed in Kwazulu Natal between 2000 and 2002. Consequently, malaria costs associated with the artemether-lumefantrine intervention alone are calculated as the *allocation factor* (as described above) multiplied by *annual health facility outpatient costs*.

4.2.4: Calculating cost-effectiveness of the interventions

Incremental costs were calculated as the difference between baseline costs and post-intervention costs for (1) the artemether-lumefantrine intervention alone and (2) both the 'artemether-lumefantrine + IRS' interventions, based on data for Manguzi sub-district and for the whole of Ingwavuma district, respectively. In scenario 1 (evaluating the artemether-lumefantrine intervention alone), data from Manguzi sub-district has been used. Since the health outcomes data for this scenario are just estimates, based on the results of the Delphi survey, analyses for this scenario have not been extrapolated to the whole district (i.e. to avoid gross errors). On the other hand, in scenario 2 (evaluation of the 2 key interventions – ACTs and improved IRS) costs and health outcomes data were extrapolated to the whole of Ingwavuma district. Cost for the IRS intervention were calculated based on the findings reported by Goodman [163] and others and those reported by Conteh and others [153] as described in section 4.3.4.3. Health outcomes (number of malaria cases, admissions and deaths for the whole of Ingwavuma

district) for scenario 2 were readily available from the Malaria Control Program in Kwazulu Natal. The total costs for scenario 2 were calculated as *unit costs* – cost per malaria case/death treated/averted – (derived from costs calculated from the sampled health facilities in Manguzi sub-district) multiplied with the number of malaria cases/deaths.

4.2.5: Sensitivity analyses

One way and multi-way sensitivity analyses were conducted to explore the impact of varying estimates for variables around which there is some uncertainty, including:

- The percentage contribution of ACT to the decline in malaria cases, admissions and deaths using the ranges of Delphi estimates;
- The annualisation rate used for capital expenditure. For South Africa, the SA Reserve Bank recommends an 8% discount rate. However, given that several studies use 3-5%, sensitivity analyses have be done to assess the impact of using a lower rate;
- The length of stay of hospitalised malaria patients, given that the hospital studied (Manguzi) has an average length of stay of 7 days while others report an average length of stay of 3 days per malaria admission;
- The impact if the price of SP had been equivalent to the international median price, instead of the inflated price actually paid by Kwazulu Natal health authorities;
- Lower prices of RDTs were considered. The current price for Paracheck® manufactured in India ($0.60) was used for the lowest cost of an RDT;
- In light of the potential for ACT prices to reduce in the near future, different prices of ACT were considered. Prices considered include:
    - The price of artesunate plus amodiaquine (Adult $1.70; 7-13 years $1.05; 1-6 years $0.70) quoted by Sanofi_Synthelabo for blister packed combination;
    - Price of Dihydroartemisinin-piperaquine estimates (Adult $1.00; Age 11-15 years $0.75; <=10 years $0.50) based on MMV quote of under $1 per adult treatment.

4.3: RESULTS

4.3.1: Results of the Household Survey

The Household survey in Kwazulu Natal was conducted in 7 sections of Ingwavuma district (see Figure 4.1). The overall objective of the survey was to collect data on malaria treatment seeking behaviour, household costs due to malaria as well as on socio-economic variables that will be helpful in understanding the area in which the ACT intervention was being implemented. The survey data was collected from 437 households and involved a total of 2509 people. The survey was conducted in a rural setting, where socio-economic indicators are relatively poor as summarised in Table 4.3.

About 51% of the households reported being less than 1 hour (of walking) away from the nearest health care facility, and 77% of the households reported being within 5km from the nearest health care facility.

Table 4.3: Selected Socio-Economic Indicators in Ingwavuma district based on household survey.

INDICATOR	DESCRIPTION
Income	28% reported zero income, Average annual income is $538 (N=602 individuals).
Use of Electricity	53% of households do not use electricity at all (N=437 households)
Employment	7% employed; 17% unemployed, 41% students, 20% preschool, (N=2509 individuals)
Highest Education level	41% ≤ Grade 2; 40% Grade 7-10 (N=2509 individuals)
Main water source	47% public tap; 20% flowing stream/rain; 3% tap on site (N=437 households)
Main source of Energy	97% use wood; 3% paraffin (N=437 households)
Toilet facilities	91% had no toilet (N=437 households)

Of a population of 2,509 people on whom data was collected during this survey, the ages of only 2038 were known, with a minimum of <1 year and a maximum of 89 years. The median age was 17.2 years. This population was 45% male and 55% female, consistent with the prevalence of men leaving rural areas as migrant workers. The levels of education were relatively low, with 33% having no schooling at all, 18% having at most Grade 2 education, 37% having Grade 7 level of education. About 17% of the population was unemployed, 41% were students, 14% were housewives, and about 20% of the population was younger than school-going age. Thus those working (mainly as subsistence workers or casual labourers on farms) comprised only 7% of the total population, since about 2% are pensioners.

Survey results show that only 3% of the households interviewed had a tap in the dwelling or on site as the main source of water, while 47% relied on getting water from a public tap, and 20% got their water from flowing streams or rain. The main sources of energy in this community were wood (97% of households), and gas and paraffin (3%). Most concerning is the finding that 91% of the households reported not having toilets, while 4% used pit latrines and 1% used chemical toilets. Most of these communities live in very basic patriarchal homesteads with 46% of the houses being grass-thatched and 51% having iron sheet roofs, and most house walls were made of either reeds (39%) or mud (29%).

For the population interviewed, expenditure on transport to the nearest health care facility was generally low, with 70% of 235 respondents spending nothing, 28% spending less than $2 and about 2% spending more than $10 on transport to facilities. For those respondents who were escorted to the facility by another person average expenditure on transport was $0.33, where 84% of the respondents' caregivers spent nothing on transport and 15% spend spent less than $2. Fourteen percent of the households spent nothing on food (subsistence farming is prevalent), 23% spent between $1 – $10, 60% of households spend between $10 – $50 every month, while only 12 households spent more than $50 monthly on food (the highest being $160). The average monthly food expenditure for all the households (including those that spend nothing) was $20.14. A summary of household monthly expenditure on main items is presented in the table below.

Table 4.4: Household expenditure on key items (Ingwavuma, Kwazulu Natal)

ITEM	Observations	Mean	Std. Dev	Min	Max
Food (monthly)	437	$ 20.14	21.91	0	160
Transport (monthly)	437	$ 3.30	55.56	0	700
Electricity (monthly)	437	$ 1.03	24.44	0	270
Water (Daily)	437	$ 0.43	15.43	0	100
Rent (monthly)	437	$ 0	0	0	0

The average monthly income in the population included in the survey was about $31.4. The high proportion of individuals with zero income was partly due to the high levels of unemployment but also because a substantial proportion of the population were children and students (who make up about 60%

of the household members surveyed). The maximum *individual* monthly income reported was $400, while 56% reported zero income. It is interesting to note that the inclusion of income from other sources (e.g. from spouses and relatives and sale of agricultural products) changes the distribution of income in the community. As shown on the table below, the inclusion of "additional income" results in a change of the proportion of people reporting zero monthly income, from 56% to 28%.

Table 4.5: Monthly income for sampled households in Ingwavuma (Kwazulu Natal)

Monthly Income **N=604**	**% of individuals reporting monthly income (%)**	**Total income = reported + additional income (%)**
$ 0	55.5	28.31
$ 1 – 20	11.9	25.5
$ 20.1 – 50.0	11.6	21.5
$ 50.1 – 100	18.1	21.4
$ 100.1 – 400	3	4

Sixty nine percent of respondents reported that they had ever suffered from malaria, and of these 98.5% had sought care for the treatment of malaria. Of the 1685 that reported having sought care, 95% reported having been cured by the treatment while 4.4% reported having not been cured. Of 235 respondents with recent malaria episodes (i.e. in the previous 2 weeks), 95% paid nothing for antimalarial drugs and 4% spent about $0.10 (presumably for pain killers). Ninety five percent paid no consultation fee for malaria treatment, while no one paid for the malaria test. About 75% reported that they paid nothing for any extra treatment-seeking activities. Ninety seven percent 97% reported having spent nothing on transport to health care facilities, while 3% had spent between $2 and $15 on transport. 48% had had at least 1 household member hospitalised for malaria. Of the 437 households, 93% spent nothing on hospitalisation, while the remaining 7% spent between $0.5 and $3.2. Of all households interviewed, only 4% of households had experienced at least one death attributed by the respondent to malaria.

Of 235 people who had recent malaria episodes the average number of sick days for all the respondents with recent malaria episodes was 4.3 days. Only 27% met the malaria control programmes target of patients seeking treatment within 48 hours of symptom onset. 93% reported having been sick for less than or equal to 7 days.

Table 4.6: Number of sick days with malaria (households in Ingwavuma, Kwazulu Natal)

Number of days sick	Frequency (N = 232)	Percent
< 1 day	5	2.2
1 day	12	5.2
2 days	47	20.3
3 days	61	26.3
4 days	25	10.8
5 days	27	11.6
6 days	5	2.2
7 days	34	14.7
10 – 16 days	15	6.5
21 days	1	0.43

4.3.2: Results of the Delphi Survey

The collection of opinions and estimates from the Delphi panel was stopped after the third round when the estimates from individuals were not changing substantially, fewer people were responding and the ranges of each estimate had narrowed. The narrowing of ranges was more a result of panellists revising their estimates accordingly as opposed to being a result of lack of response of one person in Round 3. This survey understood consensus as 'a general agreement', hence reasonable consensus was reached after round 3. The panel of experts identified four key factors as being responsible for the massive decline in malaria incidence. The factors include (i) re-introduction of spraying with DDT for traditional but not western style structures (*DDT in Kwazulu Natal*), (ii) the introduction of spraying in southern Mozambique (*IRS-Moz*), (iii) the change of first line treatment from SP to artemether-lumefantrine (*AL*), and (iv) change in climate (*Climate*). Table 4.7 provides a summary of the results of the Delphi survey in each of the three rounds. The interventions are believed to have made different contributions in the reduction of:

(a) malaria incidence [malaria cases],

(b) severe malaria [malaria admissions], and

(c) malaria mortality [malaria deaths].

Table 4.7: Estimates of the percentage contribution of different interventions to the decline in malaria notifications, admissions and deaths in Kwazulu Natal.

Table 4.7 (a): Relative contribution of factors to decline in Malaria cases

		DDT in Kwazulu Natal	IRS-Moz	AL	Climate	Other
Round 1	Average	40.8	17.1	31.8	8.8	
9 respondents	Median	36.0	15	31	1	
	Range	(10-80)	(4-40)	(0-70)	(0-32)	
Round 2	Average	40.5	14.0	32.6	8.8	4.1
9 respondents	Median	37.5	10	34.5	7.5	5
	Range	(20-80)	(7-30)	(0-50)	(0-20)	(0-10)
Round 3	Average	38.6	13.6	37.6	6.9	3.4
8 respondents	Median	40	10	36	5	5
	Range	(30-50)	(10-20)	(25-50)	(2-12)	(0-6)

Table 4.7 (b): Relative contribution of factors to decline in Malaria Admissions

		DDT in Kwazulu Natal	IRS-Moz	AL	Climate	Other
Round 1	Average	30.0	14.6	46.1	8.0	
9 respondents	Median	33.5	10.0	40.0	2.0	
	Range	(3-60)	(2-40)	(25-90)	(0-31)	
Round 2	Average	32.8	10.8	44.0	7.1	5.4
9 respondents	Median	31	10	45	5	5
	Range	(10-60)	(5-17)	(25-60)	(0-19)	(0-10)
Round 3	Average	30.9	11.0	48.7	4.0	5.4
8 respondents	Median	30	10	46	5	5
	Range	(20-40)	(5-15)	(35-60)	(0-5)	(0-10)

Table 4.7 (c): Relative contribution of factors to decline in Malaria deaths

		DDT in Kwazulu Natal	IRS-Moz	AL	Climate	Other
Round 1	Average	18.8	12.4	61.0	6.8	
9 respondents	Median	16.0	5.0	55.0	2.0	
	Range	(3-50)	(2-40)	(38-90)	(0-29)	
Round 2	Average	20.9	9.0	60.9	4.8	4.5
9 respondents	Median	21.5	7.0	60.5	4.5	5.0
	Range	(10-31)	(5-20)	(42-80)	(0-17)	(0-8)
Round 3	Average	22.1	8.7	62.0	3.1	4.0
8 respondents	Median	20	10	62	4	5
	Range	(15-30)	(5-10)	(50-70)	(0-5)	(0-8)

Taking the median values, results in Table 4.7 show that the re-introduction of DDT, followed by the change in treatment policy to artemether-lumefantrine, were the main contributory factors in reducing the number of malaria cases in Kwazulu Natal. Together these were estimated to have been responsible for 76% of the decrease in malaria cases (Table 4.7(a)). While the re-introduction of DDT is believed to have had a relatively bigger contribution (40%) in declining malaria cases (Table 4.7(a)), the change in treatment policy is believed to have been the key intervention influencing the decline in number of malaria admissions and deaths (Tables 4.7 (b) and (c)). The Delphi results also show that the introduction of IRS in Southern Mozambique was estimated to have contributed 10%, while climatic and other factors together were estimated to have contributed $\leq$10% to the decline in number of malaria cases, admissions and deaths.

4.3.3: Changes in Malaria Health Outcomes

Following the implementation of the 3 interventions, there was a decline of 93.7% in annual malaria outpatient cases from 23,186 (i.e. 19,925 at clinics + 3,261 at hospital outpatient department) at baseline (2000) to 1,453 (1,166 + 287) after the interventions (2002), a 90.8% reduction in malaria admissions from 1,902 to 175 and a 95% reduction in malaria-related deaths over the same two-year period in the sample of facilities in the Manguzi sub-district (see Table 4.8). This has been accompanied by an overall 5.1% reduction in general hospital outpatient visits, 19.5% reduction in general admissions as well as a 9.3% reduction in inpatients days at hospital level, but not at clinic level where headcounts increased by 27.9% (see Table 4.8). A greater decline in overall hospital outpatient visits and admissions following the marked decline in malaria cases and admissions was probably prevented by the increasing HIV/AIDS burden at health facilities in Kwazulu Natal (as found to be the case in Manguzi hospital during this study, with a total of 808 new HIV positive cases in 2002 alone compared to 112 in 2000). These findings of a marked decrease in confirmed malaria cases are consistent with the decrease in malaria notifications reported for the entire Kwazulu Natal Province in the national Malaria Information System. Annual confirmed malaria cases notified for the whole of Kwazulu Natal province decreased by 78% from 41,786 in 2000 to 9,443 in 2001. There was a further decrease in notifications of 75% recorded in 2002, when only 2,345 cases were notified for the entire province (Figure 4.2). In addition, there was a 95% decline in the number of malaria deaths at Manguzi hospital compared to a 70.9% increase in total hospital deaths.

These declining trends in numbers of malaria cases, admissions and deaths continued in 2003. Barnes and others report a 99% decrease in number of malaria cases and admissions and a 97% decrease in malaria-related deaths between 2000 and 2003, based on data from 3 sentinel hospitals and 10 clinics in Kwazulu Natal [177]. Malaria deaths recorded by hospitals include most of the malaria deaths that occur in the community since even deaths that occur in the community have to be reported to a hospital to obtain the death certificate required for burial, a highly-valued ceremony culturally.

Table 4.8: Change in malaria health outcomes (from facilities in Manguzi sub-district)

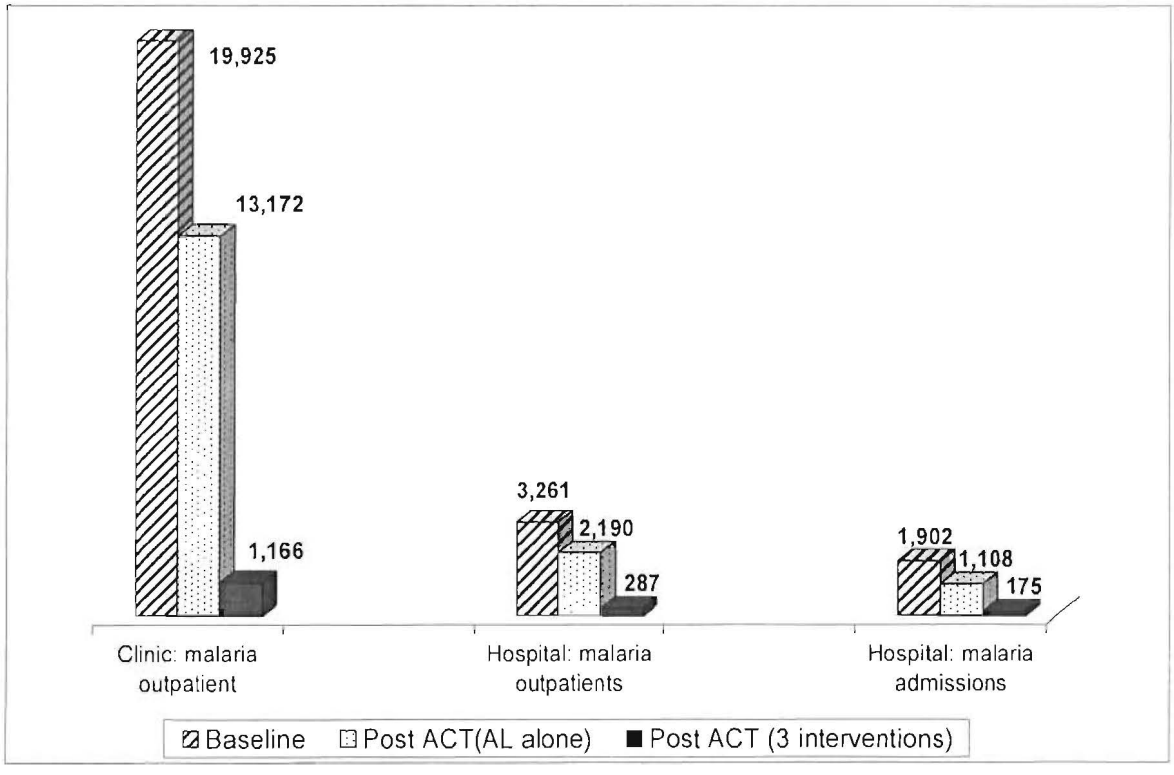
	9 Clinics (Baseline) 2000	9 Clinics (Post-intervention) 2002	*Percentage change*	1 Hospital (baseline) 2000	1 Hospital (post-intervention) 2002	*Percentage change*
Malaria outpatient cases	19,925	1,166	*-94.1%*	3,261	287	*-91.2%*
Total Headcounts	144,387	184,668	*27.9%*	45,726	43,399	*-5.1%*
Malaria cases as % of total headcounts	13.8%	0.6%		7.1%	0.7%	
Malaria Inpatient days				13,314	1,225	*-90.8%*
Total Inpatient days				74,066	67,210	*-9.3%*
Malaria Admissions				1,902	175	*-90.8%*
Total Hospital Admissions				7,485	6,029	*-19.5%*
Malaria deaths at hospital				40	2	*-95.0%*
Total hospital deaths				392	670	*70.9%*

Based on the Delphi estimates of the contribution of artemether-lumefantrine to the decline in malaria cases (36%) and malaria admissions (46%), the decline in malaria cases and admissions associated with the artemether-lumefantrine intervention alone would be substantially lower than the decline attributed to the 3 interventions (see Figure 4.3). However, it is important to note that these changes were measured only 2 years after the implementation of artemether-lumefantrine, when only the short term benefits of improved cure rates (from 12% to 99% after 42 days of follow up) and decreased gametocyte carriage[10] would be apparent. Over the medium- and long term, additional benefits of further decreases in malaria transmission and potentially delayed resistance are expected to be associated with the change in

[10] Gametocytes are the sexual stage in the malaria transmission cycle, which is responsible for infecting the mosquito. After several asexual cycles, some merozoites invade red cells and there develop into either male or female gametocytes. Gametocyte carriage refers to the existence of gametocytes in a human's blood.

treatment policy alone [24].

Figure 4.3: Changes in Malaria cases and admissions between 2000 and 2002 (Manguzi sub-district)



Source: Statistics department, Manguzi hospital (Ingwavuma, Kwazulu Natal)

4.3.4: Changes in costs (Baseline vs. Post-interventions)

4.3.4.1: Cost of implementing ACT malaria case management policy

The process of change of first line treatment and implementation of combination therapy in Kwazulu Natal involved several discussions, negotiations and consensus building meetings with key stakeholders, as well as the printing of revised treatment guidelines and training of health care providers in three districts. Collection of data on the costs of implementing the change in treatment policy was difficult because, as previously discussed, most activities were undertaken as part of routine work for the Malaria Advisory Group and the Kwazulu Natal Department of Health. For this reason, it was fairly difficult to disaggregate the costs of new policy implementation from their day-to-day expenditure. However, estimates of the costs of some of the activities, such as training workshops and printing of new treatment guidelines, were obtained and came to about US $ 7,580. This estimated total amount is for the

implementation of artemether-lumefantrine in all the malarious areas of Kwazulu Natal province.

4.3.4.2: Malaria case management costs

A summary of baseline and post-intervention malaria outpatient treatment costs is presented in Table 4.9, unit costs for malaria outpatients are presented in Tables 4.10 and 4.11, while costs for treating malaria inpatients are presented in Table 4.12.

Results presented in Table 4.9 show that there were substantive declines in expenditure on *outpatient malaria services* between the baseline and post-intervention periods, at both clinic and hospital levels, resulting in financial cost savings (see Table 4.9). This is mainly attributable to the substantive (93.7%) decline in malaria outpatient cases (Table 4.8). Table 4.9 also shows a decline in expenditure on antimalarials, despite the higher unit price of artemether-lumefantrine compared to SP monotherapy (US$ 3.24 and US$ 1.65 respectively for an adult dose[11] at 2002 prices). However, despite the marked reduction in malaria cases, expenditure on malaria diagnostics has not reduced by the same proportion because malaria still needs to be excluded in many febrile patients, although only a small proportion (8% in 2002) tested positive. '*Other recurrent expenditure*' in Tables 4.9 and 4.11 refers to health facility expenditure on personnel, consumables, maintenance, utilities, administration and other recurrent items (see Table 4.11), allocated to treatment of malaria outpatients. Other recurrent costs constitute the biggest single proportion of total malaria outpatient costs at both baseline (67%) and post-intervention (40%) phases. The narrow perspective of cost of antimalarials and diagnostics, usually considered when making decisions around changing treatment policy, is therefore not reflective of important costs associated with malaria case management. Thus, the other recurrent and capital costs associated with managing malaria cases should be carefully evaluated and taken into account when making decisions, as they constitute a relative big proportion of total costs. Particularly, personnel costs (making up 55.4% and 33.4% of total malaria outpatient costs, at baseline and post-intervention, respectively) should be considered, as the reduction in malaria cases is potentially likely to result in release of human resources for other uses (care for other patients). This is particularly relevant in areas where health workers have

[11] South Africa generally procures drugs at prices substantially higher than international median prices. The price at which KZN procured SP in 2000 (more than 20 times higher than the international median price) has been used in our analyses and has been inflated to 2002 prices. The sensitivity analysis uses the international median price.

relatively heavy workloads. Interestingly, the cost of antimalarials takes up a relatively smaller percentage (12.8% and 16.1% at baseline and post-intervention, respectively) of total treatment costs for malaria outpatients. Note that since reduction of malaria cases does not necessarily translate into financial cost-savings with these 'other recurrent and capital costs' (because they are fixed costs in the short and medium term), they have been excluded from the calculation of financial cost-savings. Overall, there was an 88.9% decline in total malaria outpatient costs, as a result of the three interventions implemented in Kwazulu Natal, as described previously.

Table 4.9: Economic costs of treatment (SP monotherapy vs. AL) for outpatient malaria cases (based on a sample of health facilities in Manguzi sub-district) (2002 US $)

Outpatient Costs (US $) 2002 prices	Clinics (9) baseline	Clinics (9) Post-intervention	*Percentage change*	Hospital baseline	Hospital Post-intervention	*Percentage change*
Antimalarial costs	25,255	3,323	*-86.8%*	4,273	819	*-80.8%*
Cost of Malaria tests	29,668	9,329	*-68.6%*	2,761	1,144	*-58.5%*
Other recurrent Exp	86,927	3,933	*-95.5%*	67,831	6,291	*-90.7%*
Capital expenditure	9,983	451	*-95.5%*	4,085	379	*-90.7%*
TOTAL malaria expenditure	**151,833**	**17,036**	*-88.8%*	**78,950**	**8,633**	*-89.1%*
Cost Savings		**42,271**			**5,071**	
Kwazulu Natal: % total reduction in malaria outpatient costs: baseline vs. ACT						**88.9%**
Kwazulu Natal: % total reduction in malaria outpatient costs attributable to AL: baseline vs. ACT						**31.8%**

Note: cost-savings are calculated on changes in costs for malaria tests and antimalarials, excluding the changes in costs of "other recurrent and capital costs".

Table 4.10 shows that there is a major difference between *cost per malaria outpatient* between the different levels of care. Outpatient unit cost at the hospital is more than 2 times higher than that at clinic level mainly because of higher unit costs of 'other recurrent' and capital costs at hospital level, and particularly because of higher personnel costs at hospital compared to clinic level (see Table 4.11). For example, while there are about 5 health and 4 non-health workers at a clinic, there are 274 health and 110 non-health workers at the hospital, and the total size of one clinic is about 300 square-metres while that of a hospital is 5,200 square-metres. 'Other recurrent and capital costs', constituted up to 64% and 91% of *cost per malaria outpatient treated* at clinic and hospital levels, respectively, at baseline (Table 4.10).

Furthermore, there are differences in unit costs between baseline and post-intervention phases, especially at the clinic level. At clinic level, there is a major (91.7%) increase in unit costs in the post-intervention phase, despite the cost savings ($47,342) achieved (Table 4.9). This is explained by the different magnitudes by which total costs and number of malaria outpatient cases have declined between the baseline and post-intervention phases. For example, at clinic level, while there was an 8.9-fold reduction in total costs, baseline *versus* post-intervention, there was a 17.1-fold reduction in number of malaria outpatient cases at clinics. In contrast, the increase in malaria outpatient unit cost at hospital level (24.2%) is not as major as that at clinic level (91.7%), because of the similar magnitude of the decline in total cost (9.1-fold) and number of malaria outpatients (11.4-fold) at hospital level between baseline and post-intervention periods.

Table 4.10: **Unit costs** of treatment (SP vs. artemether-lumefantrine) for **outpatient malaria** cases (based on a sample of health facilities in Manguzi sub-district) (2002 US $)

Outpatient Costs (US $) 2002 prices	**Clinics (9) baseline**	**Clinics (9) Post-intervention**	**Percentage change**	**Hospital baseline**	**Hospital Post-intervention**	**Percentage change**
malaria cases	19,925	1,166		3,261	287	
Cost per malaria outpatient treated (total malaria costs)	$7.62	$14.61	*91.7%*	$24.21	$30.08	*24.2%*
Antimalarial cost per outpatient treated	$1.27	$2.85	*124.9%*	$1.31	$2.85	*117.8%*
Diagnostic cost per malaria outpatient treated	$1.49	$8.00	*437.3%*	$0.85	$3.99	*371.0%*

When clinic and hospital data are combined, the total baseline outpatient malaria cost is US $230,783 (i.e. $ 151,833 at clinic + $ 78,950 at hospital outpatient) for 23,186 malaria outpatients, resulting in an average *cost per malaria outpatient visit* of US $9.95. Total outpatient costs post-intervention are US$ 25,669 (i.e. $ 17,036 at clinics + $ 8,633 at hospital outpatient) for 1,453 malaria patients, translating into an average *cost per malaria outpatient visit* of US$ 17.67. The post-intervention unit cost is higher than the baseline unit cost because of the relatively greater reduction in the number of malaria outpatient cases in relation to the reduction in total costs in the post-intervention phase.

Although less money is spent on antimalarials and diagnostics for outpatients in the post-intervention phase (compared to baseline) (Table 4.9), there are considerable differences in the amount of money spent on antimalarials and diagnostics *per outpatient treated* between baseline and post-intervention, at both clinic and hospital levels. An important finding of this analysis is that the amount of money spent on malaria diagnosis per malaria outpatient treated is likely to increase considerablely, in the short term, when malaria control and management are improved. Table 4.11 shows a 5.4-fold and 4.7-fold increase in the diagnostic unit cost at clinic and hospital levels, respectively, between baseline and post-intervention periods. This is explained by the relatively smaller reduction in total cost of diagnostics (3.2-fold and 2.4-fold at clinic and hospital levels, respectively) relative to the decline in number of malaria outpatients treated (17.1-fold and 11.4-fold at clinic and hospital level, respectively). The fact that many malaria tests have to be done to confirm malaria in substantially fewer patients (8% in 2002) and the increase in antimalarial cost per patient treated are important in contributing to the higher overall unit cost per malaria outpatient between baseline and post-intervention. For instance, while there is a decline or a slight increase in other unit costs (see Table 4.11 for the detailed breakdown) at both clinic and hospital levels, there is an overall 413% and 121% increase in the **diagnostic** and **antimalarial** *cost per malaria outpatient treated*, respectively, between baseline and post-intervention, when data for clinics and hospital outpatients are combined.

Recently, the prices of artemether-lumefantrine have declined, and the WHO preferential price for AL internationally is US$ 2.40 for an adult dose[12]. However, Kwazulu Natal has not been able to access this price as the preferential agreement with Novartis was not in place at the time Kwazulu Natal implemented artemether-lumefantrine, and subsequently Kwazulu Natal requirements are below the minimum order quantity. Thus, South Africa was paying ZAR 34 (US $3.24) for 24 tablets of artemether-lumefantrine (an adult treatment course) in 2002 and is currently (in 2004) paying ZAR 44.34 for an adult course of artemether-lumefantrine.

Table 4.11: Detailed presentation of recurrent and capital malaria outpatient costs, based on data from a sample of health facilities in Manguzi (Kwazulu Natal)

[12] Lower prices of artemether-lumefantrine and SP have been used in sensitivity analyses.

Cost Items (2002 US$)	Baseline: Clinic malaria outpatient unit costs	Post-intervention: Clinic malaria outpatient unit cost	Baseline: Hospital malaria outpatient unit costs	Post-intervention: Hospital malaria outpatient unit cost
Administration	$0.13	$0.10	$0.35	$0.37
Antimalarials	$1.27	$2.85	$1.31	$2.85
Equipment & Furniture	$0.04	$0.04	$0.03	$0.03
Kitchen/Catering			$0.04	$0.04
Malaria diagnosis	$1.49	$8.00	$0.85	$3.99
Laundry			$0.04	$0.04
Maintenance	$0.10	$0.08	$0.17	$0.18
Medical Consumables	$0.44	$0.34	$1.14	$1.21
Other Recurrent Expenditure	$0.01	$0.01	$0.34	$0.35
Personnel	$3.47	$2.68	$17.99	$18.96
Transport			$0.43	$0.45
Utilities	$0.16	$0.13	$0.26	$0.28
Capital Costs	$0.50	$0.39	$1.25	$1.32
Total	**$7.62**	**$14.61**	**$24.21**	**$30.08**

Table 4.11 shows that personnel costs accounted for the largest proportion (55.4%) of total malaria outpatient costs at baseline, followed by diagnostics (14%), antimalarial costs (12.8%) and capital costs (6%). For the post-intervention phase, personnel costs are 33.4% of total outpatient malaria costs, while diagnostics, antimalarials and capital costs take up 41%, 16.1% and 3.2% respectively. On average, except for diagnostic costs, the unit costs associated with management of malaria cases are higher at hospital compared to clinic level, the biggest difference being in personnel costs where the hospital unit costs (for the personnel line item) is 30 and 40 times higher than that for the clinic level, at baseline and post-intervention respectively.

Table 4.12 shows that there has also been a substantive decline in expenditure on *malaria inpatient services* because the number of malaria inpatient-days reduced drastically (by 91%), resulting in further financial cost savings. It is important to note that malaria management for inpatients has not changed since 2000, i.e. they still receive Quinine for 7 days[13], and hence these cost savings are attributable to

[13] Hospital malaria admission for 7 days on average is practiced at the hospital studied, but it is not generalisable to all hospitals.

the massive reduction in number of malaria admissions. It is important to add, however, other factors could contribute to the reduction in cases of severe malaria (e.g. improvement in treatment seeking behaviour and changes in host risk factors like pregnancy and infancy).

Despite the massive cost-savings realised between the baseline and post-intervention periods, changes in unit costs were not substantial. On average, there was an increase in overall *cost per inpatient-day* from $24.99 to $29.03 (Table 4.12) because the number of malaria inpatient-days reduced drastically (by 91%). While there was a substantial increase in the *diagnostic cost per malaria inpatient-day*, as with decreased malaria transmission more negative diagnostic tests are performed for every positive test, the changes in *antimalarial costs per malaria inpatient-day* were not large (see Table 4.12). There were neither changes in the drug used for inpatients (quinine) nor in the average length of stay (7 days), so no change in antimalarial costs was expected. The increase from $0.54 to $0.74 can be explained by the changes in clinical practices for management of malaria inpatients. For the post-intervention phase, in addition to treating with Quinine, all malaria inpatients (except pregnant women) were also given Doxycycline.

Table 4.12: Inpatient malaria cases management costs (sub-district level) (2002 US $)

Inpatient Costs (US $) 2002 prices	1 Hospital: baseline	1 Hospital: post-intervention	***Percentage reduction***
Antimalarial costs	7,198	907	*-87.4%*
Cost of Malaria tests	4,830	2,093	*-56.7%*
Other recurrent Exp	289,830	29,425	*-89.8%*
Capital expenditure	30,892	3,132	*-89.9%*
TOTAL malaria expenditure	**332,750**	**35,557**	*-89.3%*
Cost Savings (US $)		9,028	
No. of admitted patients	1,902	175	
In-patient days	13,314	1,225	
ALOS	7	7	
cost per malaria inpatient day (*total costs*)	**$24.99**	**$29.03**	
antimalarials cost per inpatient-day	$0.54	$0.74	
Diagnostic cost per inpatient-day	$0.36	$1.71	

4.3.4.3: Cost of insecticide residual spraying in Kwazulu Natal

Goodman and others estimated a *cost per person covered* of ZAR14.605 for spraying all house structures in Ingwavuma with Deltamethrin in 1999 [163]. Conteh and others estimated a *cost per person covered* of US$ 1.5 for spraying with DDT in Southern Mozambique (under the *Lubombo Spatial Development Initiative*, a regional spraying program that covers the Ingwavuma area) in 2000 [153]. Estimates of *per person costs* of spraying with Deltamethrin and DDT (in Kwazulu Natal in 2000) have been calculated on the basis of the Goodman et al.'s estimate of ZAR14.605 (1999 prices) and the Conteh and others' *cost per person covered* estimate of spraying with DDT of US $1.50 (2000 prices), as described earlier in the methods section. In the study area, approximately 60% and 40% of the homesteads were sprayed with Deltamethrin and DDT respectively in 2000. *Cost per person covered* of "*spraying with deltamethrin and DDT*" was estimated to be ZAR16.00 (2002 prices), which translates into US$ 1.524 *per person covered*. These costs include costs of personnel, vehicles, equipment, training, supplies, insecticide and storage, but exclude the costs of project management, monitoring and surveillance.

Table 4.13 shows a reduction in spraying costs between 'baseline' and 'post-intervention' periods. This is mainly because the price of DDT insecticide is much lower than that of Deltamethrin. For example, Conteh and others quote a 2000 price of $5.30 for DDT compared to $66 for the synthetic pyrethroid ICON®, while the costs of carbamates are $72.5 for FICAM® and $25 for Propoxur® [153]. Similarly, the international median 2004 prices reported from WHO are $3.00 ($2.50 - $3.50) for DDT compared to $9.5 ($7.00 - $12.00) for the synthetic pyrethroid Deltamethrin 5% wettable powder [178]. The finding that overall costs of spraying with DDT are relatively lower than those of spraying with other insecticides have also been reported in an IRS program in Southern Mozambique, where spraying with FICAM and Propoxur cost 2.3 times more than spraying with DDT [153].

Table 4.13: Economic costs of spraying in Ingwavuma district in 1999 and 2000 (2002 US $)

	Cost/p/covered (ZA Rand)	Inflator	Cost/p/covered (2002 ZA Rand)	Population estimate	Total costs (2002 Rand)	Total cost (2002 US$)
Deltamethrin (1999) (*Baseline*)	14.605 (1999)	1.264	18.461	178,695	3,298,838	**314,175**
Deltamethrin (60%) and DDT (40%) (2000) (*Post-intervention*)	16.003 (2002)	1	16 003	182,342	2,918,019	**277,907**

Notes:

- Cost/person covered in 1999 obtained from Goodman et al (2001b).
- Cost/person covered in Ingwavuma for 2002 has been estimated based on Goodman et al's 1999 estimates for spraying with Deltamethrin in Ingwavuma and Conteh et al's 2000 estimates cost of spraying with DDT in Southern Mozambique.
- Population estimates for Ingwavuma are based on 1996 census data increased by the estimated population growth rate.
- Inflators are based on the CPIX figures published by Statistics South Africa.
- An average exchange rate of R10.5=US$1 has been used for the year 2002.

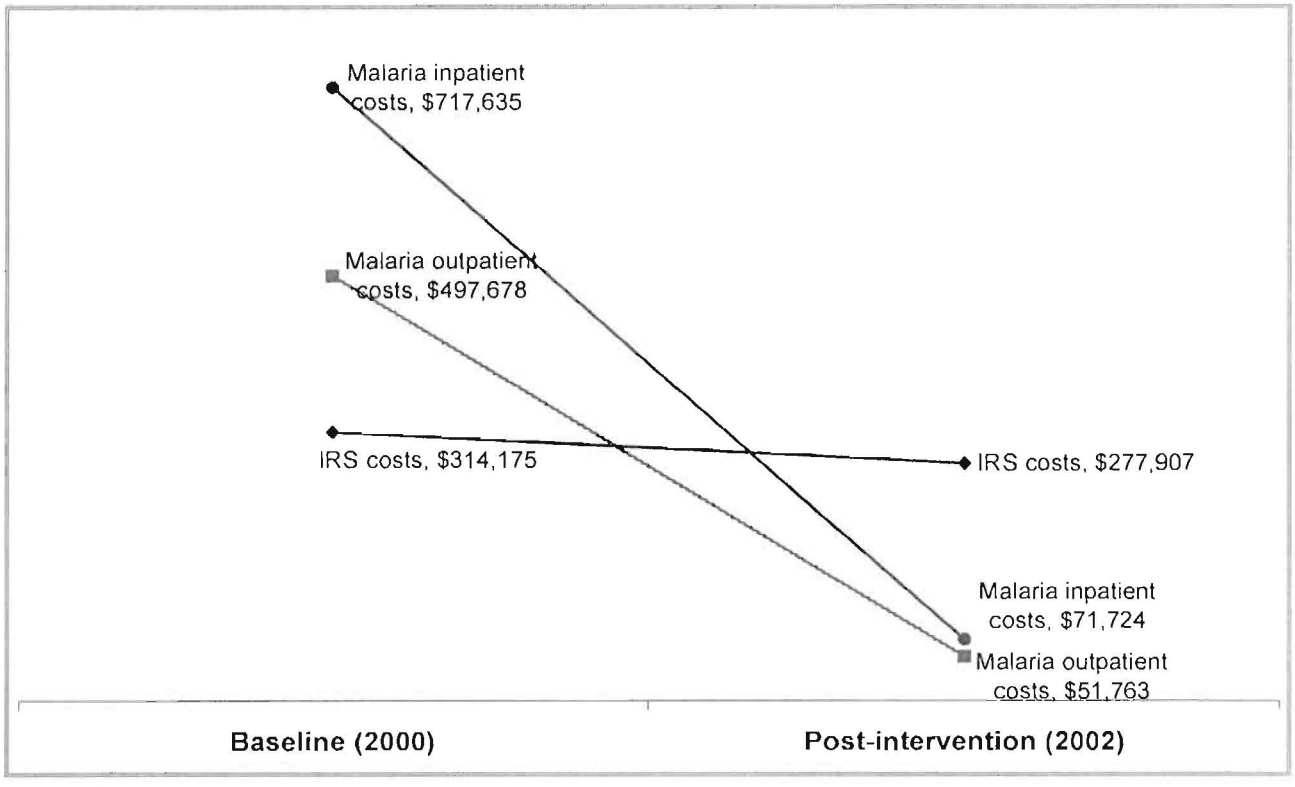
4.3.4.4: Combined cost of treatment and spraying in Ingwavuma district

Figure 4.4 provides a summary of the breakdown of the economic costs of spraying and treatment, for baseline and post-intervention periods, for the whole of Ingwavuma district. Malaria case management costs data previously presented were scaled up from the 10 sampled health facilities (9 clinics and 1 hospital) in Manguzi sub-district to calculate treatment costs for the whole of Ingwavuma district at baseline and post interventions. Costs of managing outpatient and inpatient malaria cases at baseline, for the whole district, were calculated as unit costs (derived from sample of health facilities as presented Tables 4.9, 4.10 and 4.11) multiplied by the total number of cases for the whole district (obtained from the National Department of Health). This assumes that the unit costs obtained from sampled facilities are representative of the whole district, and that both rural district hospitals in Ingwavuma admitted patients for 7 days.

From Figure 4.4, the baseline total cost of combined IRS and provision of treatment at outpatient and inpatients levels (US$ 1,529,489) is considerablely higher than the post-intervention costs of IRS and treatment at outpatient and inpatient levels (US$ 401,394), resulting in some financial cost-savings and/or release of resources for other uses, associated with the combined 'interventions' of using artemether-lumefantrine for first line treatment and improving vector control by using DDT for IRS of

traditional homesteads in Ingwavuma. Further, Figure 4.4 indicates that inpatient costs account for the largest proportion of cost-savings, followed by outpatient costs while there is a small change in IRS costs.

Figure 4.4: Costs of IRS & malaria case management in Ingwavuma district (2002 US $)



4.3.5: Cost Effectiveness of Interventions

4.3.5.1: Cost-effectiveness of artemether-lumefantrine in Kwazulu Natal

As outlined in section 4.3.2, the Delphi survey indicated that the two interventions considered the most important contributory factors to the reduction in malaria cases, admissions and deaths in Kwazulu Natal between 2000 and 2002 were the change of first line treatment policy and re-introduction of IRS with DDT for traditional homesteads. Improved vector control through community based IRS in neighbouring southern Mozambique was considered the third most important contributor to decreased malaria morbidity in Kwazulu Natal. Results from the Delphi survey attributed a median contribution of 36% (range 25-50%) and 46% (range 35-60%) to the decline in malaria cases and malaria admissions respectively, to ACT implementation alone. The survey attributed a median of 40% (range 30-50%) and 30% (range 20-40%) to the decline in malaria cases and malaria admissions respectively, to the re-

introduction of DDT alone. Details of the total costs, unit costs and cost saving associated with the change to artemether-lumefantrine alone, based on the median Delphi estimates are calculated in Table 4.14 to include a sensitivity analysis using the ranges of the Delphi estimates.

Table 4.14: Evaluating the artemether-lumefantrine intervention alone (based on Manguzi sub-district sample)

BASELINE (Treat with SP for Outpatients and with Quinine [7days] for inpatients)						
		Total Cost (2002 US $)	Cases or inpatient-days	Unit cost (2002 US $)		
Kwazulu Natal	Malaria outpatient services	230,783	23,186	9.95		
	Malaria inpatient services	332,750	13,314	24.99		
Post ACT (Treat with AL for Outpatients and with Quinine [7days] for inpatients)						
		Malaria outpatient cost	Number of cases	Average cost/malaria outpatient	Reduction in costs (2002 US$)	ICER
Kwazulu Natal	Malaria outpatients (100% change)	25,669	1,453	$17.67	205,114	$9.44
	Adjusted for 36% due to AL (median)	**157,440**	**15,362**	**$10.25**	**73,343**	**$9.37**
Sensitivity analysis	Adjusted for 25% due to AL (lower range)	180,729	17,753	$10.18	50,054	$9.21
	Adjusted for 50% due to AL (upper range)	127,450	12,320	$10.34	103,333	$9.51
		Malaria inpatient cost	No. of malaria inpatient days	Average cost/malaria inpatient-day	Reduction in costs (2002 US$)	ICER
Kwazulu Natal	Malaria inpatient-days (100% change)	35,557	1,225	$29.03	297,193	$24.58
	Adjusted for 46% due to AL (median)	**196,168**	**7,753**	**$25.30**	**136,583**	**$24.56**
Sensitivity analysis	Adjusted for 35% due to AL (lower range)	225,917	9,083	$24.87	106,834	$25.25
	Adjusted for 60% due to AL (upper range)	156,794	6,061	$25.87	175,956	$24.26

NOTES:
1. Malaria cases and costs have been calculated based on estimates of % contribution of AL to decline in malaria cases and admissions (obtained through a Delphi survey). Ranges have been used for sensitivity analyses.
2. Figures for malaria outpatient services combine the outpatient costs and health outcomes at both clinic and hospital.

Table 4.14 shows that the 'intervention' of changing from SP monotherapy to artemether-lumefantrine alone would have resulted in improvement in health outcomes (in terms of reduced malaria cases and admissions), as well as reduction in costs, even when the most conservative estimates of changes in health outcomes (25% and 35% for cases and admissions, respectively) are considered. In standard

economic evaluation, this situation of *dominance* is most desirable because the intervention being evaluated (artemether-lumefantrine) 'dominates' its comparator (SP monotherapy) since it results in reduced costs and, at the same time, improved health outcomes. In a situation of dominance, the ICER figures presented in Table 4.14 should be interpreted as "reduction in malaria costs for every malaria case averted". Following this, if it is true that artemether-lumefantrine is responsible for about 36% and 46% of the decline in malaria cases and admissions, respectively, between 2000 and 2002, then Kwazulu Natal would reduce malaria costs by US$ 9.37 and US$ 24.56 for every malaria outpatient case and malaria inpatient-day averted, respectively.

Furthermore, sensitivity analyses indicated that if Kwazulu Natal had previously paid a substantially lower price for SP (i.e. the international median price[14]), the cost savings would have been lower, but would not have been lost, even when one considered the lowest possible estimate of artemether-lumefantrine contribution (25%) to the decline in malaria cases. On the other hand, cost-savings would have been higher if Kwazulu Natal had been able to procure artemether-lumefantrine at the WHO preferential price (U$ 2.40 per adult treatment instead of the US$ 3.24 actually paid). Total reduction in costs for outpatient malaria services with lower prices of SP and artemether-lumefantrine are shown in Table 4.15.

Table 4 15: Sensitivity analyses of cost savings based on prices of SP and AL (using data from Manguzi sub-district)

	Base Case	Lower Price of SP	Lower Price of AL
Price of SP (2000 prices)	$2.296	$0.623	$2.40
Reduction in costs (if 100% attributable to AL)	$205,114	$178,818	$206,186
Reduction in costs (if 36% attributable to AL)	$73,343	$47,047	$74,961
Reduction in costs (if 25% attributable to AL)	$50,054	$23,758	$51,914
Reduction in costs (if 50% attributable to AL)	$103,334	$77,038	$104,644

Multi-way sensitivity analyses indicate that the key findings of AL being cost effective and cost saving remain unaltered when the values of variables, around which there is some uncertainty, are varied (see Table 4.16). Although there is a relatively broad range in the value of estimated reduction of malaria costs, none of the sensitivity analyses change the finding that the introduction of artemether-lumefantrine

[14] The International Median Price was obtained from the Management Sciences for Health International Drug Price Indicator Guide website (http://erc.msh.org/dmpguide/). The median price of SP across suppliers cited in the Guide in 2000 was inflated by 15% for insurance and transport, as recommended by MSH.

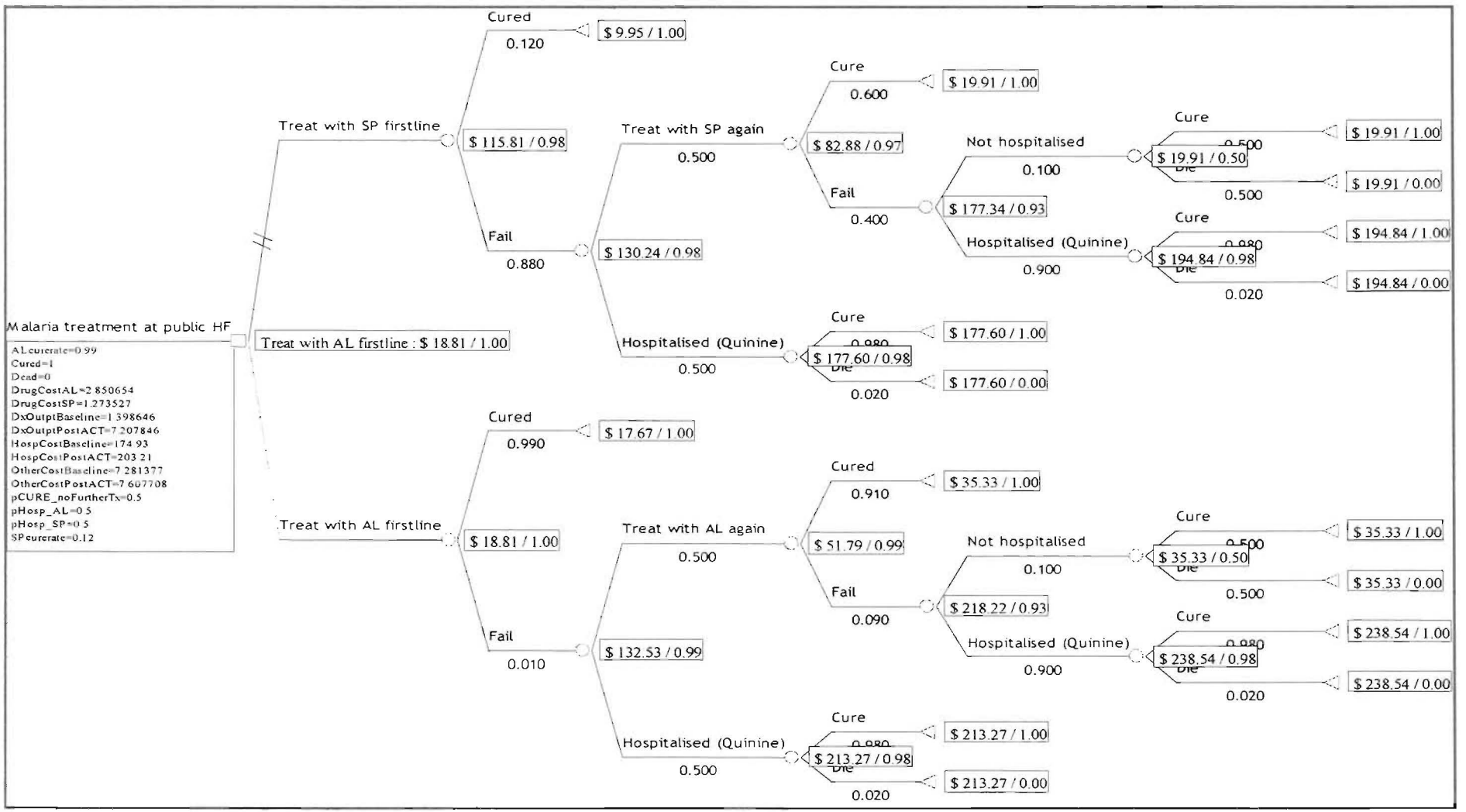
as the first line malaria treatment in Kwazulu Natal has resulted in some cost savings and the unit cost estimates change very little.

Table 4.16. Multi-way sensitivity analysis results (annualisation rates; average length of inpatient stay and contribution of artemether-lumefantrine to decline in malaria cases and admissions)

	Lowest estimates	Highest estimates
Cost per malaria outpatient	**$10.09**	**$10.57**
Variable assumptions	3% annualisation rate for capital; 25% contribution of AL to decline in malaria cases	8% annualisation rate for capital; 50% contribution of AL to decline in malaria cases
Reduction in malaria outpatient care costs	**$50,054**	**$103,334**
Variable assumptions	8% annualisation rate for capital; 25% contribution of AL to decline in malaria cases	8% annualisation rate for capital; 50% contribution of AL to decline in malaria cases
Inpatient-day unit cost	**$24.91**	**$26.10**
Variable assumptions	3% annualisation rate for capital; 35% contribution of AL to decline in malaria admissions; 7 days average length of stay	8% annualisation rate for capital; 60% contribution of AL to decline in malaria admissions; 3 days average length of stay
Reduction in malaria inpatient care costs	**$106,834**	**$179,937**
Variable assumptions	8% annualisation rate for capital; 35% contribution of AL to decline in malaria admissions; 7 days average length of stay	8% annualisation rate for capital; 60% contribution of AL to decline in malaria admissions; 3 days average length of stay

4.3.5.2: Cost-effectiveness of first line antimalarials in KZN using a decision tree model

Figure 4.5: Decision tree results comparing SP monotherapy and artemether-lumefantrine in Kwazulu Natal



The cost-effectiveness of the ACT intervention has also been evaluated using a simple decision tree model. As described in the methods chapter (chapter 3), a decision tree was used to evaluate and compare the relative impact of SP monotherapy and artemether-lumefantrine on costs and health outcomes associated with both uncomplicated and severe malaria. The descriptions of variables used in the model and their assigned values have been presented in Table 3.6 (Chapter 3). As noted earlier, the malaria case management intervention in Kwazulu Natal (whether using SP monotherapy or artemether-lumefantrine) is part of an integrated malaria control strategy in Kwazulu Natal that includes effective vector control and routine use of definitive diagnosis. In the decision tree model, the artemether-lumefantrine and SP treatment alternatives are evaluated in the context of the existing vector control initiatives. It is important to note that the costs of vector control have not been included in the decision tree analysis, however, the case management-related costs used in the model were calculated based on the health outcomes prevailing in the context of vector control (i.e. for both the SP and AL phases). The results of the decision tree analysis, presented in Figure 4.5, show that artemether-lumefantrine is clearly more cost-effective relative to SP monotherapy. Results in Table 4.17 confirm the findings reported earlier in Table 4.14 which show that the artemether-lumefantrine intervention results in reduced costs and/or cost savings and improved health outcomes. Thus, since the SP monotherapy option is dominated, incremental cost-effectiveness ratios cannot be calculated.

The cost-effectiveness ratios obtained from the analysing the decision tree model are interpreted as the overall *cost incurred per patient cured of malaria* (that is, cost per life saved) regardless of whether they are treated as outpatients with a first line drug or as inpatients with second line drugs. Given this, results in Table 4.17 show that with the overall *cost per malaria patient cured* for the artemether-lumefantrine alternative is $18.82, while SP monotherapy has a substantially high *cost per patient cured* of $ 118.26.

Table 4.17: Summary of cost-effectiveness results (*cost per patient cured*) from the Kwazulu Natal decision tree model

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E
Treat with AL firstline	$ 18.8		0.9999		$ 18.82	
Treat with SP firstline	$ 115.8	$ 97.0	0.9792	-0.0206	$118.26	(Dominated)
Dominance Report:						
The strategy "Treat with SP firstline" is dominated by "Treat with AL firstline".						

Table 4.18: Values used for sensitivity analyses in the Kwazulu Natal decision tree model

Variable	Value used in Kwazulu Natal tree	sensitivity analyses lowest value	sensitivity analyses highest value
ALcurerate	0.99	0.12	0.99
SPcurerate	0.12	0.12	0.99
Cured	1		
Dead / Die	0		
DrugCostAL	$2.85	$1.00	$3.24
DrugCostSP	$1.27	$0.20	$2.30
DxOutptBaseline	$1.40	$0.50	$2.00
DxOutptPostACT	$7.21	$0.50	$7.21
HospCostBaseline	$174.93	$74.97 (3 days)	$174.93 (7 days)
HospCostPostACT	$203.21	$87.09 (3 days)	$203.21 (7 days)
OtherCostBaseline	$7.28	$0.00	$10.00
OtherCostPostACT	$7.61	$0.00	$10.00
pCURE_noFurtherTx	0.5	0.1	0.8
pHosp_AL	0.5	0.1	0.8
pHosp_SP	0.5	0.1	0.8

Sensitivity analyses of the decision tree model consistently confirm that artemether-lumefantrine is more cost-effective relative to SP monotherapy even when the values of different variables are varied over a wide range of values (Table 4.18). Results of the sensitivity analyses of the decision tree model, presented in Table 4.19, confirm that even when the 'worst case' scenarios are considered (i.e. when the values of variables used are in a favour of the SP monotherapy option), the cost-effectiveness ratio of the artemether-lumefantrine option remains substantially lower than that of the SP monotherapy option, except in the event where cure rate of SP monotherapy is higher than that of artemether-lumefantrine (which is not rational given the degree to which resistance to SP monotherapy has spread).

Table 4.19: Result of the sensitivity analyses of the decision tree model for Kwazulu Natal

Sensitivity analyses results	SP monotherapy option	AL option
Cost effectiveness ratio	**$118.26**	**$18.82**
Variable assumptions	Base case	Base case
Cost effectiveness ratio	**$143.52**	**$19.30**
Variable assumptions	*pHosp_SP* = 0.8	*pHosp_AL* = 0.8
Cost effectiveness ratio	**$84.43**	**$19.17**
Variable assumptions	*pHosp_SP* = 0.1	*pHosp_AL* = 0.1
Cost effectiveness ratio	**$57.18**	**$18.19**
Variable assumptions	*HospCostBaseline* calculated for 3 days of hospitalisation	*HospCostPostACT* calculated for 3 days of hospitalisation
Cost effectiveness ratio	**$118.26**	**$18.82**
Variable assumptions	*HospCostBaseline* calculated for 7 days of hospitalisation	*HospCostPostACT* calculated for 7 days of hospitalisation
Cost effectiveness ratio	**$116.68**	**$16.96**
Variable assumptions	Lowest antimalarial (SP) cost per malaria outpatient = $0.2	Lowest antimalarial (AL) cost per malaria outpatient = $1.0
Cost effectiveness ratio	**$119.77**	**$19.21**
Variable assumptions	Highest antimalarial (SP) cost per malaria outpatient = $2.3	Highest antimalarial (AL) cost per malaria outpatient = $3.2
Cost effectiveness ratio	**$116.94**	**$12.08**
Variable assumptions	Lowest baseline diagnostic cost per malaria outpatient = $0.5	Lowest post ACT diagnostic cost per malaria outpatient = $0.5
Cost effectiveness ratio	**$119.15**	**$18.82**
Variable assumptions	Highest baseline diagnostic cost per malaria outpatient = $2.0	Highest post ACT diagnostic cost per malaria outpatient = $7.2
Cost effectiveness ratio	**$110.83**	**$11.21**
Variable assumptions	Other cost per malaria outpatient excluded from the analysis (i.e. other costs = 0)	Other cost per malaria outpatient excluded from the analysis (i.e. other costs = 0)
Cost effectiveness ratio	**$118.26**	**$120.13**
Variable assumptions	Lowest effectiveness of SP monotherapy (i.e. cure rate = 12%)	Lowest effectiveness of AL (i.e. cure rate = 12%)
Cost effectiveness ratio	**$11.16**	**$18.82**
Variable assumptions	Highest effectiveness of SP monotherapy (i.e. cure rate = 99%)	Highest effectiveness of AL (i.e. cure rate = 99%)

NOTE: the cost of effectiveness ratios would be similar at $74.89 and $74.25, for SP monotherapy and artemether-lumefantrine, respectively, when their cure rates are 46.8% and 51.2%, respectively.

Results in Table 4.19 show that the C/E ratios for the two treatment options are sensitive to changes in some of the variables. For example, the C/E ratio for the SP option is sensitive to changes in the values of *pHosp_SP* (i.e. the probability that a patient who has failed to get cured with SP (first time) will seek care at a hospital and will be hospitalised to get second line treatment), *HospCostBaseline* (i.e. cost of treating one malaria inpatient which includes diagnostic, drugs and other costs at baseline), the inclusion or exclusion of 'other recurrent and capital costs' in the analysis, and to changes in the cure rate of SP. The lower the value of *pHosp_SP*, the lower the C/E ratio and vice versa for the SP option. Similarly, results also show that the C/E ratio for SP will be substantially lower if malaria patients are only hospitalised for 3 days instead of 7 days. As expected the exclusion of 'other costs' results in a lower C/E ratio for SP, and vice versa, and the higher the cure rate of SP the lower its C/E ratio. Similarly, the C/E ratio for the artemether-lumefantrine option is sensitive to changes in the values of the same variables (i.e. *pHosp_AL*, *HospCostPostACT*, and cure rate for artemether-lumefantrine) in the same way. In addition, the cost-effectiveness ratios for SP and artemether-lumefantrine are sensitive to changes in the prices of the antimalarials and to changes in the diagnostic costs. Notable is the finding that the C/E ratio for the artemether-lumefantrine option is highly sensitive to the exclusion of 'other costs' (i.e. $11.21 compared to $18.82 when the other costs are included), and to the changes in the diagnostic costs. Figures 4.6 and 4.7 show that the C/E ratio for AL steadily increases as diagnostic costs and 'other costs' increase. Although Figure 4.7 shows that change in C/E ratio for AL option is not very big when the 'other costs' are set at $10 per malaria outpatient, major increases in 'other costs', if as high as $100 per malaria outpatient, would result in equally large changes in the C/E ratio ($111. 20) for the artemether-lumefantrine option (Figure 4.8). Figure 4.8 brings out the importance of increasing the value of the variables over a wider range. This scenario has been hypothetically considered since 'other costs' are not expected to be as high as $100. However, it is important to note that C/E ratio for the artemether-lumefantrine option remains substantially lower than that for the SP option even at the highest values considered for these variables.

Figure 4.6: Sensitivity analysis on diagnostic costs malaria outpatients after ACT implementation

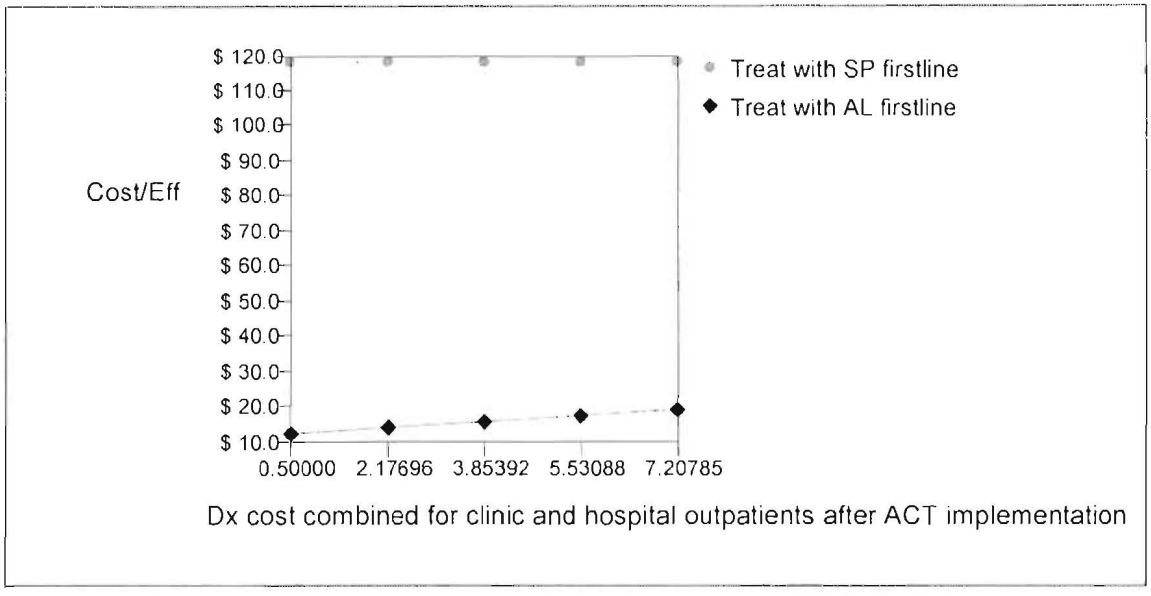


Figure 4.7: Sensitivity analysis on 'other costs of treatment' for malaria outpatients post ACT implementation

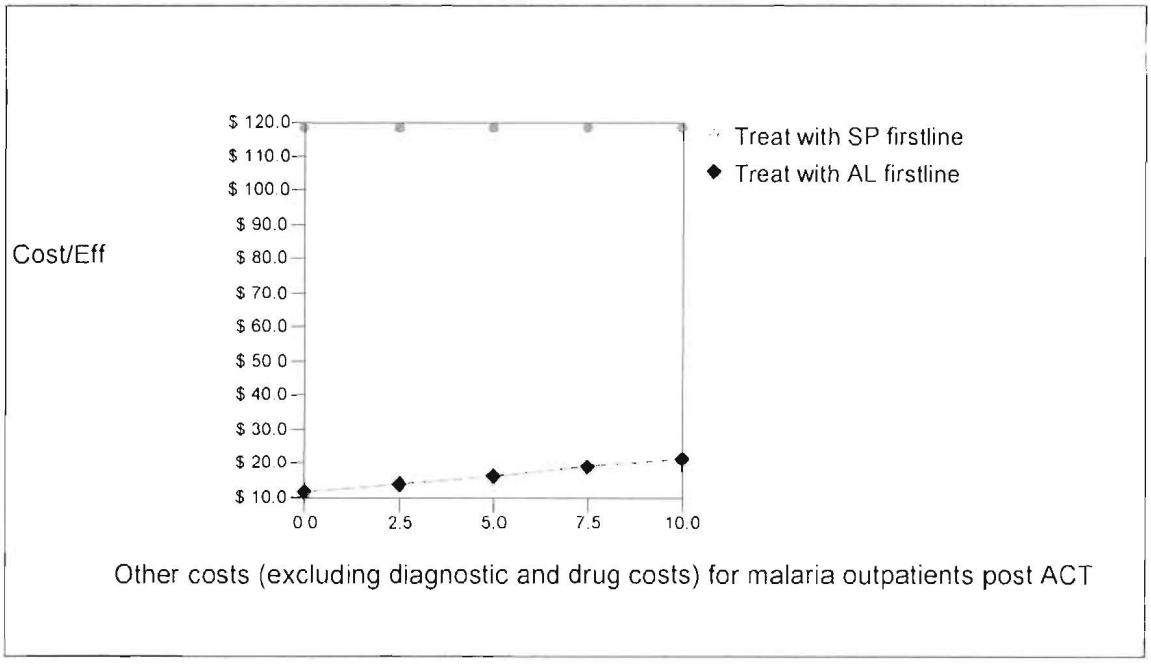
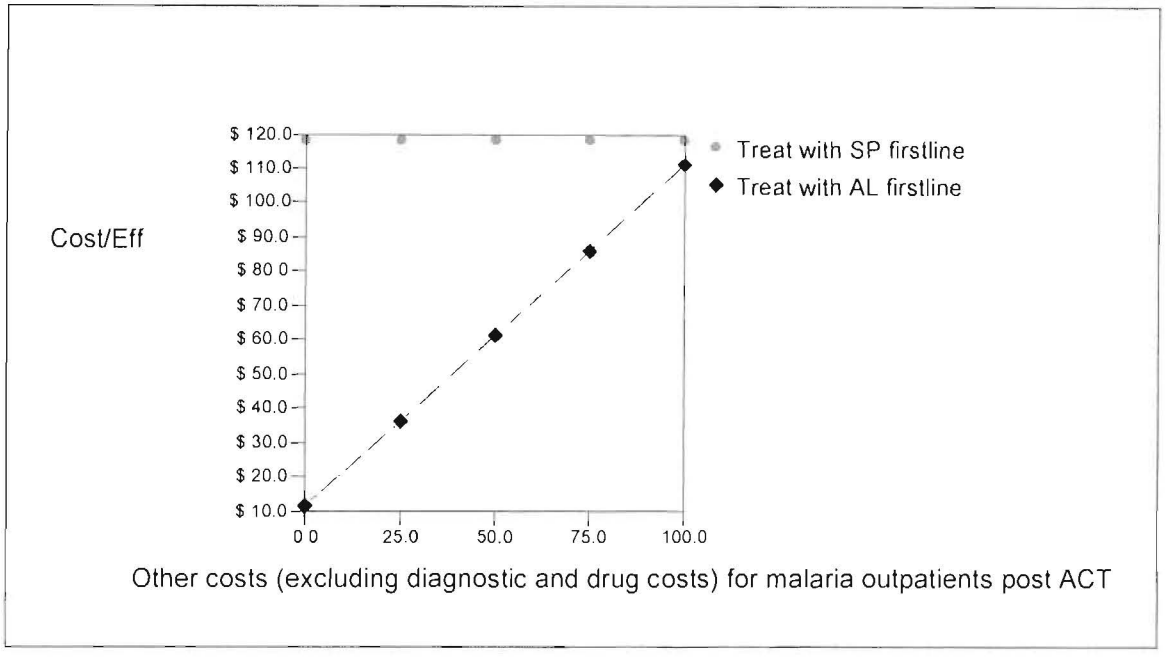


Figure 4.8: Sensitivity analysis using a very high value for "other costs" per malaria outpatient post ACT



4.3.5.3: Cost-effectiveness of the combined intervention (Changes in both Drug policy and in IRS) in Ingwavuma District, Kwazulu Natal

Table 4.20 presents the change in malaria health outcomes and the associated costs extrapolated for the whole of Ingwavuma district. This evaluation considers the ***actual*** malaria cases and admissions based on data collected for 2000 and 2002. Results in the Table 4.20 show substantive cost savings (of over US$ 1.1 million) associated with all the interventions that contributed to the massive decline in malaria transmission in Kwazulu Natal. However, results of the Delphi survey indicate that the two combined interventions alone are estimated to have resulted in a 76% decline in both malaria cases and admissions over the two-year period, in which case the cost savings would be $867,478.

Table 4.20: Evaluating impact of combined interventions (for Ingwavuma district)

		Manguzi sample: Cost (2002 US $)	Cases / admissions (sampled facilities)	Average cost per case (sample)	Confirmed district cases / admissions	Total district cost (2002 US$)
	IRS with Deltamethrin (whole district)	$314,175				314,175
Baseline 2000	Treating with SP (outpatient)	$230,783	23,186	$9.95	50,000	497,678
	Treating with Quinine (Inpatient)	$332,750	1,902	$174.95	4,102	717,635
					TOTAL	1,529,489
	IRS with Deltamethrin and DDT (whole district)	$277,907				277,907
Intervention 2002 [76% reduction] *(40% for IRS + 36% for AL)*	Treating with artemether-lumefantrine (outpatient)	$70,870	6,669	$10.63	14,227	151,190
	Treating with Quinine (inpatient)	$109,576	589	$185.89	1,253	232,914
					TOTAL	662,011
	IRS with Deltamethrin and DDT (whole district)	$277,907				277,907
Intervention 2002 *(sensitivity analysis: overall observed decline)*	Treating with artemether-lumefantrine (outpatient)	$25,669	1,453	$17.67	2,930	51,763
	Treating with Quinine (Inpatient)	$35,557	175	$203.19	353	71,724
					TOTAL	401,394

4.3.6: Study Limitations

A limitation in the analysis of costs of antimalarials in Kwazulu Natal is the lack of reliable data on the quantities of antimalarials actually consumed. Despite extensive attempts to get accurate data on quantities of antimalarials dispensed in the health facilities studied, it was not possible to get complete data from either the clinics or the hospital. For purposes of this analysis, estimates of quantities of antimalarials dispensed were calculated on the basis of appropriate dosages and number of malaria patients seen by age group at each clinic in a year. The assumptions with this method are that, all patients were treated with SP+CQ (at baseline) and with artemether-lumefantrine (after policy

change), and that the correct dosage was given for all patients. This is not an unrealistic assumption, given the fact that the findings of the exit interviews and observations made at various clinics in Kwazulu Natal confirm that 92% of patients were treated with adequate doses of antimalarials (SEACAT Drug Utilisation Study report, 2001, unpublished). An additional 15% of artemether-lumefantrine and SP was added to the estimated quantity of antimalarials issued to take into consideration wastage due to vomiting and shrinkage.

There is a limitation in the way the actual cost of spraying with Deltamethrin and DDT in Kwazulu Natal in 2000 has been calculated. Since the actual costing of the IRS program in Kwazulu Natal was beyond the scope of this study, the cost of indoor residual spraying in Kwazulu Natal was calculated using the *per person covered* spraying costs estimate for 1999 (when Deltamethrin alone was used) and the *per person covered cost* of spraying with DDT in southern Mozambique for 2000 (since both Southern Mozambique and Kwazulu Natal were being sprayed under the same Program). The assumptions made are that cost of spraying with Deltamethrin in 2000 would not change much compared to those in 1999, especially given that a greater proportion (60%) of the homesteads was sprayed with Deltamethrin. The cost of spraying the remaining 40% of the homesteads with DDT in Kwazulu Natal (in 2000) is assumed to be similar to the cost of spraying with DDT in Southern Mozambique.

Another limitation of the analyses presented in this chapter is around the estimation of cost of change of policy. As previously described, costs of undertaking activities specific to the change of treatment policy could not be easily separated from the day-to-day costs of the institutions involved in implementing the new policy, especially since these activities were undertaken as part of routine work. As a result of this, the estimated cost presented and discussed in this chapter is not representative of the total costs incurred, and most importantly, it is not representative of what countries with different malaria control activities would incur.

Further, cost-effectiveness results presented in this chapter are partly based on the results of a simple decision tree model. The biggest limitation of the model is that it is relatively simple and may not fully reflect the actual situation of malaria epidemiology. For example, the treatment outcomes considered of either being cured, failing treatment or dying as a result of treatment leave out the

possible outcome of being cured of malaria but leaving one with neurological sequalae that impairs the patients' lives substantially. Such health outcomes have been excluded from the model because they are difficult to measure and there isn't much empirical evidence on the probabilities associated with such outcomes. Also, there are limitations around the type of model chosen for the analysis. The most suited type of model given the malaria epidemiology is the Markov model. A Markov model is more complicated and requires extensive information. Since the focus of this thesis is not economic modelling, a simple decision tree model for which information was relatively easier to collect was used to establish whether the same conclusions on cost-effectiveness of artemether-lumefantrine would be reached using different methods of analysis. Further, the model implicitly assumed a perfect and efficient health provision system which is neither the case in the study site nor in other malaria-endemic countries, as wastage, shrinkage and expiry of drugs are common place. Lastly on the decision tree model, some of the variables (especially probabilities) for which it was difficult to get information based on empirical evidence, values were arbitrarily assigned, although extensive sensitivity analyses were undertaken.

There is a limitation posed by the study design used for this evaluation. There are arguments that before-and-after studies may not be able to adequately confirm that the observed changes are exclusively due to the intervention and that no other factors have contributed to the changes observed between the baseline and the evaluation of the intervention. Essentially, the before-and-after design was used because the intervention being evaluated was being widely implemented in the whole province. For this reason, it was not feasible to obtain an adequate 'control site' in Kwazulu Natal. Given the high level of SP resistance it would not have been ethical to delay the change in treatment policy in a "control site". Thus, the type of evaluation conducted in Kwazulu Natal can be classified as an 'adequacy impact evaluation' [159], which aims to make inferences about the adequacy of the malaria interventions (described in this chapter) in reducing malaria cases and thus malaria costs compared to baseline conditions. This approach to evaluation has a major limitation in the sense that there is no control group and hence it is rather difficult to infer that observed improvements are due to the interventions being evaluated [159] and not any other factors. However, efforts have been made to address the problem of lack of a control group. Firstly an international Delphi survey was used to evaluate the contribution of each component of the malaria control programme in Kwazulu Natal. A similar evaluation was conducted in Mpumalanga (as discussed in chapter 5) which has several

similarities that allow for comparison, but also differences that help in validating some of the findings and methodologies used for the Kwazulu Natal evaluation. It is considered highly unlikely that other changes in the study sites could have contributed to the large changes in malaria case numbers observed in both Kwazulu Natal and Mpumalanga. For instance, there were no changes in the health care systems and the malaria control programmes in the study sites (except for the re-introduction of DDT in Kwazulu Natal, whose impact has been adequately addressed in the evaluation). The possible impact of climatic changes was not considered substantial by the Delphi panellists. However given this study design limitation, the plausibility of the results needs to be interpreted within the context of the study being conducted in an area of effective vector control.

Lastly, there are some limitations around the Delphi survey. While the panel consisted of international experts in various fields of malaria, more panellists were specialists in the area of vector control relative to other categories of speciality. In addition, all panellists were presented with information on trends in malaria cases (i.e. Figure 4.2) in the first round of collecting opinions and estimates. It is possible that these two factors had an influence on the kind of responses obtained on the contribution of the different factors on the decline in malaria cases, particularly the apparent relative bias towards higher estimates for IRS.

4.4: DISCUSSION AND CONCLUSIONS

Early results on the impact of malaria control policy changes in Kwazulu Natal suggest a synergy between improved vector control and ensuring widespread use of artemisinin-based combination therapy (ACT). While it is difficult to separate the individual impact of these interventions, Figure 4.2 highlights that IRS is a critical component of the Kwazulu Natal malaria control program and that the reintroduction of DDT is considered to have contributed substantially to the recent decline in malaria in this province.

The changes in malaria health outcomes, notably the reduction in malaria outpatient cases and hospital admissions result in efficiency gains, following improved IRS and case management (using artemether-lumefantrine). Despite the massive reduction in malaria outpatient cases at both clinic

(94%) and hospital OPD (91%), total outpatient cases increased at clinic level (by 28%) and declined slightly at hospital level (5%) between 2000 and 2002. This implies that had there not been a marked decline in malaria outpatient cases, health facilities would have been over-burdened with higher numbers of outpatient visits, and hence health workers would have had higher workloads. For instance, if the number of malaria outpatient cases reported in 2000 had remained the same in 2002, at hospital level, the annual workload of a health worker (professional nurse) at a hospital OPD would have increased from 538 to 546 outpatient cases, while annual workload at clinic level would have substantively increased from 6,016 to 8,476 outpatient cases. In fact, even with the marked decline in number of malaria cases at clinic level, annual workloads for professional nurses (in charge of the clinics) increased from 6,016 to 7,696 (between 2000 and 2002). At inpatient level, the annual number of admissions per doctor would have increased from 936 to 970 and annual admissions per senior professional nurse from 356 to 369, between baseline and post-intervention periods, had the number of malaria admissions in 2000 remained the same in 2002. Obviously, the workloads in 2002 would be much higher than these if the increasing trends in number of malaria cases observed between 1997 and 2000 had continued (Figure 4.2). Such increases in staff workloads are likely to have resulted in reduced staff motivation and probably reduced quality of care. On the other hand, if the workload of the staff in these health facilities has been relatively low (by national or international standards), marked reductions in malaria cases and admissions would result in lower workloads and hence greater inefficiencies.

The findings also highlight the greater effectiveness and substantial cost savings associated with the change to artemether-lumefantrine. The findings of this economic evaluation show that the artemether-lumefantrine first line treatment policy is not only more cost-effective than SP monotherapy, but that it has also resulted in cost savings in the Kwazulu Natal context. This finding holds even if the most conservative estimates of the relative contribution of the change in drug regimen are used, and if the highly inflated prices of SP paid by Kwazulu Natal are replaced with international median prices. Results of a decision tree model confirm that artemether-lumefantrine is considerably more cost-effective than SP monotherapy. In fact, the decision model results confirm that the artemether-lumefantrine alternative results in both cost savings and improved health outcomes. These cost savings resulted primarily from the decrease in the total number of malaria cases and the number of malaria hospital admissions, (i.e. from improved clinical cure rates and

decrease in malaria transmission) achieved with the use of artemether-lumefantrine and improved vector control. As noted earlier, the cost savings and reduction in malaria costs (which reflect efficiency gains) are to some extent a result of reductions in expenditure on antimalarials, but most importantly are due to major reductions in expenditure on other recurrent and capital costs, particularly on personnel costs which constituted up to 55.4% of total malaria outpatient costs. The fact that staff workloads increased between 2000 and 2002, despite the massive reductions in number of malaria cases, highlights the importance of including "other recurrent and capital costs" in economic evaluations, showing that these "'other recurrent and capital costs" reflect a big proportion of resources used in providing malaria treatment services. The Kwazulu Natal findings on declining malaria cases are consistent with the improved cure rates and decreased malaria transmission associated with the widespread use of ACT in northwest Thailand [24, 81]. A 47% decline in malaria cases was observed within 1 year of the introduction of ACT (Artesunate plus Mefloquine) in northwest Thailand, which increased to a six-fold reduction over ten years. The similar experience of marked public health benefits in western Thailand suggests that the Kwazulu Natal findings reported here reflect the benefits of artemisinin-based combination therapy, rather than being specific to artemether-lumefantrine. The area studied in the western border of Thailand is similar to Kwazulu Natal with a low intensity of malaria transmission and high levels of access to antimalarial therapy, which is relatively strictly regulated.

Cost-effectiveness and affordability of ACTs is one of the issues of considerable debate around the replacement of traditional cheaper antimalarials with ACTs as first line treatment for uncomplicated malaria. Findings of this study confirm that ACTs can be cost-effective, even in the short term, in the context of low transmission of malaria, existence of a reasonable health infrastructure and concurrent additional malaria control interventions (such as IRS), high coverage with use of ACTs and strict regulation on use of other mono-therapies, and restriction of ACTs to patients who have been confirmed as having malaria using definitive diagnosis. Similar conclusions have been reached by several authors [15, 68, 152] who have demonstrated the potential cost-effectiveness of ACT in the medium- and long-term.

Findings presented in Figure 4.4 underscore the importance of having effective vector control as part of the overall malaria control strategy. Figure 4.4 shows that both IRS and improved case

management strategies come at a price. While the changes in costs of IRS are not extensive, between baseline and post-intervention phases, costs associated with the management of both uncomplicated and severe malaria decline enormously as a result of improved malaria transmission. Hence the magnitude of the results achieved as a result of the combined effect of improved case management and improved vector control through IRS would not have been achieved with only one of the strategies. Noteworthy is the impact of these combined strategies on number of malaria admissions and the malaria inpatient-related costs. The improved IRS and artemether-lumefantrine strategies are directly targeted at reducing the number of cases of uncomplicated malaria through reduced infective mosquito bites, improved cure rates and reduced gametocyte carriage and potentially through the extended useful therapeutic life of the antimalarial. As a result of this, although the inpatient treatment policy and practices remained unchanged in Kwazulu Natal, considerable costs savings were obtained from substantial reductions in the number of malaria admissions.

Results of the decision tree model bring out a clear comparison between the two antimalarial options (SP monotherapy vs. artemether-lumefantrine) in the context of vector control. Clearly, the artemether-lumefantrine alternative, in the context of improved vector control in Kwazulu Natal and in neighbouring southern Mozambique, is more cost-effective than its comparator. Although the decision tree has not been used to evaluate the cost-effectiveness of artemether-lumefantrine in the absence of improved vector control, alternative methods of analysis have demonstrated that artemether-lumefantrine would have still remained highly cost-effective and cost-saving even in the absence of improved vector control in Kwazulu Natal and vector control in southern Mozambique. This difference in cost-effectiveness ratios is particularly marked when the cure rate for SP monotherapy is as low (12%) and the cure rate for artemether-lumefantrine as high (99%), as it was in Kwazulu Natal, although in the sensitivity analysis the dominance of AL (over SP monotherapy) persists until its cure rate is only 52% compared to an SP cure rate of 47%.

Short-term cost-effectiveness of ACTs is highly dependent on key factors including: the cure rate of the existing monotherapy antimalarials, coverage with ACT use (i.e. proportion of the population who need antimalarials who actually get ACTs), level of development and capacity of health infrastructure to implement and monitor use of ACTs and to ensure minimised use of monotherapy drugs, price of ACTs, restriction of ACTs to those definitively confirmed as having malaria, and patients' compliance

with treatment regimens. It is recommended that ACT should be co-formulated or at least co-packaged to improve compliance and minimise the use of monotherapy. In the longer term, the extent to which these therapies sustain decreased malaria transmission and limit international resistance will be important.

Despite the methodological challenges associated with the cost-effectiveness analysis of ACTs, particularly in the context where confounding factors make it rather cumbersome to quantify actual impact of the ACT intervention, techniques such as Delphi survey have proved helpful in addressing these methodological challenges.

5. COST-EFFECTIVENESS OF ACTS: COMPARING ARTESUNATE PLUS SP IN MPUMALANGA WITH ARTEMETHER-LUMEFANTRINE IN KWAZULU NATAL

5.1: INTRODUCTION

As a result of increasing resistance to drugs and insecticides, malaria in South Africa became a serious problem in 2000. It was obvious that this problem would only get worse with time, if effective measures to curb the growth and spread of resistance were not put in place. Between 1995 and 2000 notification of confirmed malaria cases increased in all three provinces in South Africa where malaria transmission occurs, reaching epidemic levels in 1999 and 2000, although this increase was most marked in Kwazulu Natal (see Figure 5.1).

Findings of the cost-effectiveness of malaria control interventions; in particular the change of treatment policy to an ACT, in Kwazulu Natal showed that artemether-lumefantrine was both cost-saving and cost-effective even in the short run. However, it cannot be assumed that the Kwazulu Natal findings can be generalised to the rest of South Africa, let alone to other contexts (as will be discussed in Chapter 7). Additional evaluations of ACTs in different contexts with e.g. lower SP failure rates, no changes in vector control and a different ACT would be helpful in providing more robust conclusions on the cost-effectiveness of ACTs. For this reason, the cost-effectiveness of another ACT, artesunate plus SP (AS+SP) in a slightly different contextual setting (Mpumalanga province) was assessed and the findings of these two studies compared. Although the two study sites are similar enough to allow for meaningful comparison, there are key differences, which include:

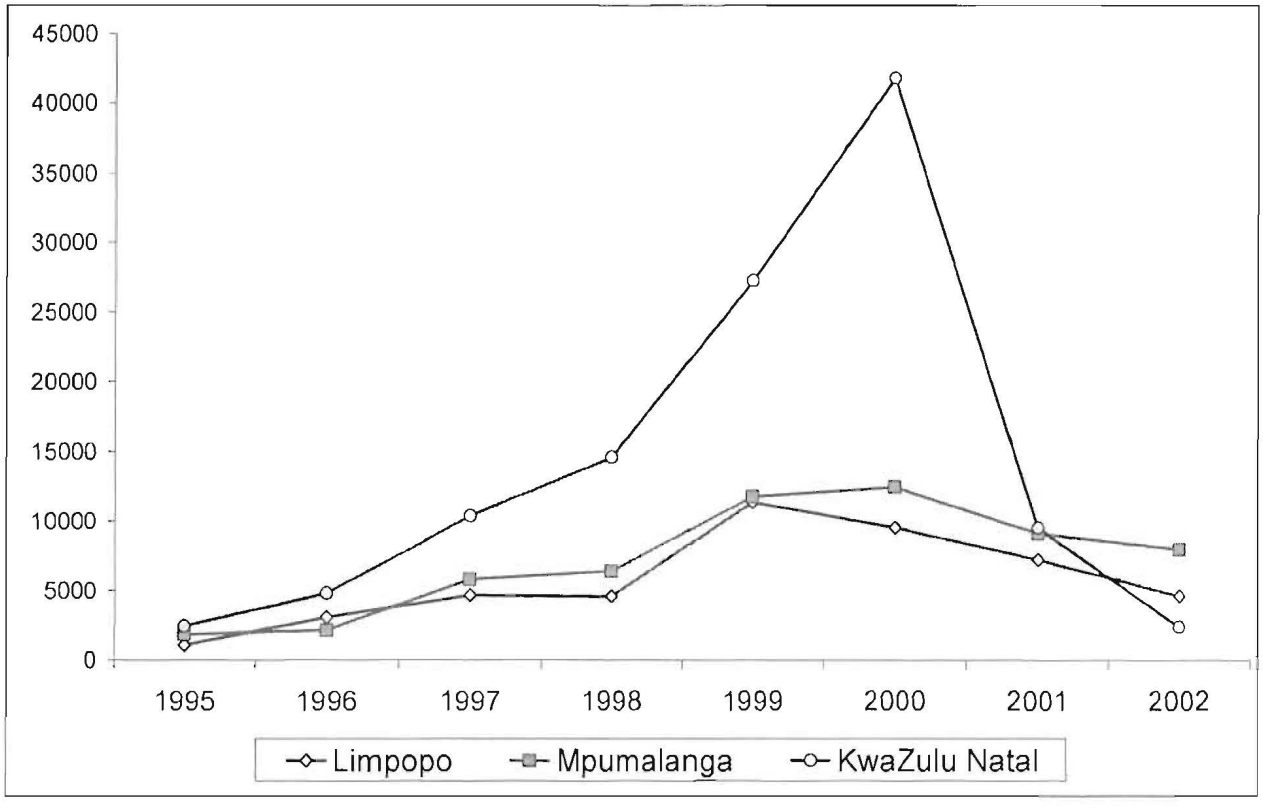
- ★ While the efficacy of SP monotherapy in Mpumalanga was high (90%) at the time of the change, SP was dismally failing in Kwazulu Natal (with efficacy of 12%).
- ★ Increasing vector resistance to pyrethroids used for IRS in Kwazulu Natal necessitated the re-introduction of spraying with DDT (almost at the same time as the change to ACTs), while insecticides remained unchanged in Mpumalanga.
- ★ New vector control initiatives in neighbouring Mozambique are more likely to benefit Kwazulu Natal (which is geographically situated closer to districts initially receiving IRS in southern Mozambique) than they are to benefit Mpumalanga.

- ★ Lastly, prior to the change to ACTs, unlike Kwazulu Natal, Mpumalanga had more conservative admission policies for malaria patients, where some cases of uncomplicated malaria were also admitted for inpatient care.

Malaria transmission in Mpumalanga is of very low intensity and is seasonal. Mpumalanga has much lower malaria incidence levels compared to Kwazulu Natal, with the highest prevalence area (Tonga district) having about 15 – 45 cases per 1,000 population. Sulphadoxine-Pyrimethamine (SP), first introduced as first-line treatment in Mpumalanga in 1997, compared with the earlier introduction in Kwazulu Natal in 1988. Quinine (oral and/or IV) remains the second line treatment for complicated/severe malaria. In Mpumalanga resistance to SP was still low at the time of change of first line treatment policy. The findings of the baseline in vivo studies conducted in 2002 showed that, of 149 patients with uncomplicated malaria who completed 42 day follow up, the cure rate for SP monotherapy was 90%. Only 2 patients (1.3%) were early treatment failures and recrudescence occurred in only 13 patients (8.7%) [162, 179]. However gametocyte carriage had increased almost 3 fold since SP implementation, prompting the change in treatment policy. At the time of the baseline economic evaluation studies, Mpumalanga's official treatment guidelines for uncomplicated malaria suggested the use of SP monotherapy. However, due to the increased number of severe malaria cases and deaths, facilities sometimes used oral quinine, together with SP, to treat outpatient cases and also opted to admit some uncomplicated cases for inpatient care if they were considered high risk (e.g. children under 2 years, pregnant women and patients recently treated with SP).

Following the high levels of treatment failures associated with the SP monotherapy as first line treatment in Kwazulu Natal in 2000 and the documented global evidence on the rapid spread of resistance to traditional antimalarials, all the 3 of South Africa's malarious provinces started investigations and dialogue on the need to change to ACTs. Kwazulu Natal province was the first province to change from SP monotherapy to artemether-lumefantrine (Coartem®) in January 2001, followed by Mpumalanga province which changed from SP monotherapy in January 2003. As SP monotherapy was still effective in Mpumalanga, the ACT selected for Mpumalanga was artesunate + SP (initially as co-packaged Arsudar®), a relatively cheaper ACT compared to artemether-lumefantrine. The choice to combine SP with artesunate aimed at 'protecting' SP (an affordable antimalarial) while it was still highly effective.

Figure 5.1: Annual confirmed malaria cases notified between 1995 and 2002 in Limpopo, Mpumalanga and Kwazulu Natal provinces, South Africa.

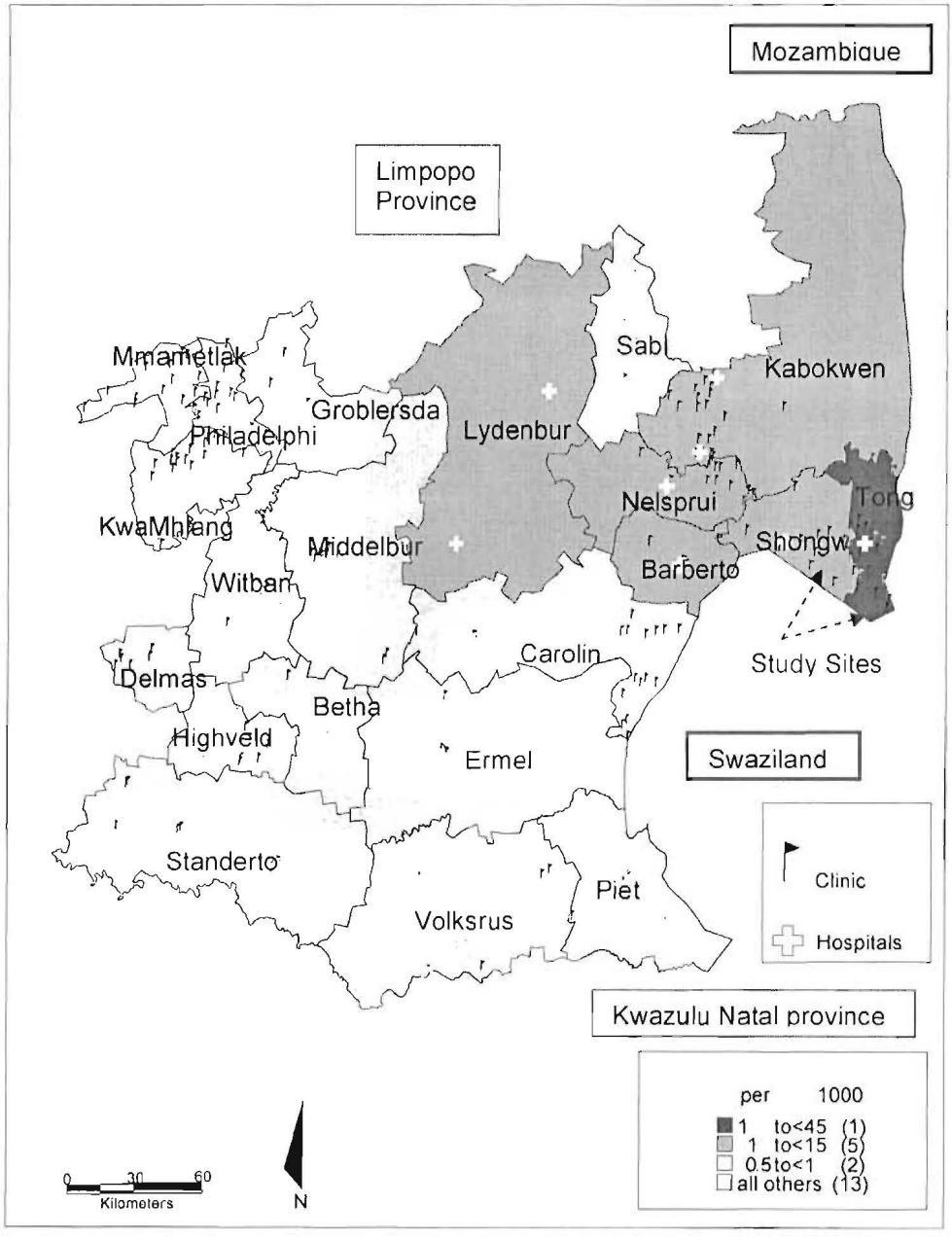


The economic evaluation study sites, Tonga and Shongwe districts, are located in eastern Mpumalanga. Tonga district is generally rural with a population of about 140,000 people. The SEACAT Household survey of 391 households with 2,280 household members in Tonga and Shongwe districts found high levels of unemployment; of those aged 18-60 years most are unemployed (35.1%), 15.3% are agricultural labourers, 16.4% are students and 12% are housewives (Castillo M, unpublished report). These levels of unemployment are consistent with the socio-economic indicators in this area showing low levels of education attainment, low levels of income and lack of proper basic services and needs, such as clean water, electricity and proper sanitation.

Figure 5.2 shows that Mpumalanga borders with Swaziland, Mozambique and other South African provinces. As there is no malaria transmission in the areas of Kwazulu Natal that border with Mpumalanga, it can be argued that there was limited impact of the Kwazulu Natal interventions to the Mpumalanga study sites (Tonga and Shongwe) – See Figures 3.1 and 5.2. However, the areas

studied in Mpumalanga (especially Tonga district) partly borders southern Mozambique (Zone 2) (see Figures 5.2 and 6.1). There is a limited potential for the IRS intervention has some impact on malaria transmission in Tonga district. However, this impact is expected to be relatively minimal, compared to the impact the IRS intervention on southern Mozambique had on Kwazulu Natal malaria transmission because of the extent of the proximity of the borders in these 2 provinces, in relation to southern Mozambique.

Figure 5.2: Map of Mpumalanga Province showing Tonga and Shongwe districts



The findings of the cost-effectiveness of malaria control interventions, and in particular artemether-lumefantrine, in the Kwazulu Natal context were presented and discussed in the previous chapter. As highlighted in chapter 4, the economic evaluation of artemether-lumefantrine in Kwazulu Natal was fraught with difficulties given the concurrent implementation of two key malaria control strategies alongside the artemether-lumefantrine intervention. Fortunately, the implementation of ACTs in Mpumalanga is not confounded by concurrent changes in vector control strategies, and because of the geography the effects of vector control in Kwazulu Natal would not spill over into Mpumalanga.

This chapter presents and discusses the findings of an economic evaluation study undertaken to assess the whether or not the introduction of AS+SP in Mpumalanga is a cost-effective intervention. In addition, this chapter aims to present and compare the findings of two economic evaluation studies, where two different ACTs have been evaluated in two different sites. As in the case of Kwazulu Natal (chapter 4), the economic evaluation of ACTs in Mpumalanga was undertaken after the change in policy was implemented, in order to asses the appropriateness of the decision to change policy and also to provide evidence for future decision-making and for other countries facing similar decisions. The results presented in this chapter evaluate and compare the costs and cost-effectiveness of artemether-lumefantrine and AS+SP in Kwazulu Natal and Mpumalanga, respectively. The conclusions reached in this chapter will help in validating the methods used in calculating, and the conclusions reached on the cost-effectiveness of artemether-lumefantrine in Kwazulu Natal (see sections 4.3 and 4.4 of chapter 4). Also, the findings in this chapter will provide a basis for some generalisation of the findings on cost-effectiveness of ACTs, since they allow for comparisons between ACTs that are differently priced.

The rest of this chapter is structured as follows: section 5.2 describes the methods used that are specific to the evaluation of AS+SP in Mpumalanga. Results of the cost-effectiveness of AS+SP in Mpumalanga and the comparison with the findings on cost-effectiveness of artemether-lumefantrine in Kwazulu Natal, as well as the study limitations for the Mpumalanga evaluation are presented and discussed in section 5.3. Section 5.4 provides a summary of the discussion and conclusions on the key findings.

5.2: METHODS

The general economic evaluation methods used across the two study sites have been described in chapter 3 and will not be repeated here. Details of the economic evaluation perspective, number of health facilities studied, sampling techniques used and methods for the measurement of health outcomes are described in chapter 3 (section 3.2.2). However, methods specific to the Mpumalanga study site due to the contextual setting of the study sites will be described in this section.

The collection of economic evaluation baseline data (compiling data for the year 2000) and the household survey in Mpumalanga took place in May 2001, while the follow-up data collection phase was undertaken in 2003 after the implementation of AS+SP. For consistency, the facilities that were studied at baseline are the same facilities that were studied post-ACT, in both Kwazulu Natal and Mpumalanga. Similarly, consistency in methods used in measurement of health outcomes, costs and cost-effectiveness was maintained across the two study sites and phases.

Tonga has a total of 15 clinics and 1 district hospital and Shongwe district has 17 clinics and 1 district hospital. Although a sample of 7 health facilities were physically visited during this study, data for all 32 clinics and 2 district hospitals were obtained from the Health District office and were used in the analyses presented and discussed in this chapter. Types of data collected and the sources of data are summarised in the Table 5.1 below.

Table 5.1: Types and Sources of Data - Mpumalanga

Type of data	Source/method of collection
Clinic Level	
Expenditure (recurrent and capital)	Nelspruit Head Office (Department of Health)
Total PHC headcounts	Tonga and Shongwe District Health Offices
Number of malaria cases	Nelspruit Head Office (Department of Health)
No. of staff at each clinic and their activities/duties	Interviews at clinics
Malaria trealment methods for uncomplicated malaria	Interviews at clinics
Quantities of antimalarials drugs dispensed in year	Stock cards at clinic for each antimalarial
Size of the facility	Physically measured (for the 3 clinics visited)
Equipment & furniture	Physical counts
Hospital Level	
Expenditure (recurrent and capital)	Financial Management System Reports 2000 obtained from Head Office (DoH), Nelspruit
Total outpatient headcounts	Hospital records
Number of malaria outpatients	Hospital records
Total number of admissions	Hospital records
No. of malaria admissions	Hospital records
Total no. of inpatient days	Hospital records
No. of malaria inpatient days	Hospital records and interviews with key staff
No. of malaria deaths	Hospital records
No. of staff & their activities/duties	Hospital records & interviews with relevant staff.
Malaria treatment practices	Interviews with relevant staff & hospital records.
Quantities & prices of antimalarials drugs dispensed	Hospital pharmacy and VUNA drug Depot
Size of the facility	Measured from plan for Tonga & Shongwe hospitals
Equipment & furniture	Physical counts & inventories

5.2.1: Conducting the Household Survey in Kwazulu Natal

The methods for conducting the household survey in Mpumalanga are described in chapter 3 (section 3.2.1).

5.2.2: Calculating health outcomes

Unlike the Kwazulu Natal study where a Delphi survey had to be used to estimate the health outcomes associated with the use of AL, measurement of health outcomes for the Mpumalanga study was more straightforward. The changes in malaria health outcomes since 2001 are believed to be

primarily a result of the impact of using a more effective first line drug that reduces malaria transmission by decreasing malaria carriage (AS+SP). This allowed the changes in the intermediate health outcomes observed in the evaluation year to be attributed to the use of AS+SP alone. The health outcomes considered included: number of (1) outpatient malaria cases, (2) malaria admissions and inpatient days, and c) malaria deaths. In addition, number of malaria cases cured and malaria cases averted have been considered.

5.2.3: Calculating Cost-effectiveness

In Mpumalanga the intervention being evaluated was AS+SP relative to SP monotherapy. In addition to calculating unit costs for both baseline and post-intervention periods, incremental cost effectiveness for AS+SP relative to SP was calculated as the change in annual malaria costs divided by the change in annual number of malaria cases.

5.3: RESULTS

The findings presented in this section mainly refer to the findings on treatment-seeking behaviour (as studied from the household survey), costs, effectiveness and cost-effectiveness of AS+SP in the Mpumalanga context. The findings presented and discussed in this section are based on data obtained from a sample of public sector health facilities (clinics and district hospitals) in the 2 districts (Tonga and Shongwe) with the highest malaria prevalence in Mpumalanga. Since the study aims to calculate unit costs related with the treatment of malaria and the cost-effectiveness of SP and AS+SP, the analyses relied on data from a sample of health facilities, thus excluding the need for extrapolation to cover the entire province of Mpumalanga. By contrast, in the Kwazulu Natal context, there was need for extrapolation to the whole of Ingwavuma district to assess the combined impact of improved case management and improved vector control. In this chapter, the Mpumalanga findings are compared with the findings on treatment-seeking behaviour, and with findings on costs, effectiveness and cost-effectiveness of artemether-lumefantrine in the Kwazulu Natal context, which have been presented and discussed in detail in chapter 4.

5.3.1: Results of the Household Surveys: comparing Kwazulu Natal and Mpumalanga

Results from the household surveys showed that both provinces had reasonable access to health care facilities with the average distance to the nearest facility being 3.8 km (2.5 – 5.1) and 6.5 km (5.9 – 7.1 km), in Mpumalanga and Kwazulu Natal respectively. This difference could have been entirely accounted for by the difference between universal sampling in Kwazulu Natal and purposive sampling in Mpumalanga, which could bias sampling in favour of those households nearer to a public clinic. However a previous study found that 69% of the population in northern Kwazulu Natal lives within 5 km of a clinic[15], while 95% are estimated to do so in Mpumalanga (Marlize Booman, Mpumalanga Department of Health, *Personal Communication*). Similarly, the duration of travel to clinics is longer in Kwazulu Natal (mean 90 minutes; 51% < 1 hour) than Mpumalanga (mean 33 minutes).

This relatively high level of access, together with the provision of free health care in almost all public health care facilities, are expected to have contributed to the finding that public clinics are the most common first source of malaria treatment for the majority of household members in Mpumalanga (93.7%) and Kwazulu Natal (71%). These proportions increase to 96.5% and 97% in Mpumalanga and Kwazulu Natal, respectively when those seeking treatment at other public health care facilities (district hospitals or Malaria Control Programme Field Camps) are included. The small remainder sought treatment either in the private sector or at a traditional healer. These findings confirm the validity of this economic evaluation being conducted from the perspective of the public sector provider.

Adherence with SP monotherapy, as a single stat dose taken under observation at the health care facility, is expected to be high unless patients elect not to accept treatment. However, achieving adequate adherence with AS+SP that requires AS treatment to be continued at home, especially once symptoms have resolved, becomes more challenging. Adherence becomes pivotal in ensuring that the expected benefits of artemisinin-based combinations are realised. Given the importance of this factor, adherence to malaria treatment was assessed in four ways during the household survey. Firstly, all household heads were asked what malaria treatments they had at home. Secondly,

[15] Unpublished Report, Medical Research Council Malaria Program (1997)

duration of malaria treatment taken by household members who had ever suffered from malaria was recorded. Thirdly, those that had suffered from malaria in the past four weeks, in whom recall bias was expected to be less were also asked whether they had any antimalarial treatment remaining and later in the interview whether they had completed the full course of treatment. Triangulation of results from each of these questions provides insight into the probable levels of adherence in the study communities.

In South Africa, drugs are tightly regulated and antimalarials can only be dispensed by registered health care facilities to patients with a prescription. Consequently, treatment found at home is most likely be those medicines remaining when a full treatment course is not completed. Very few households admitted keeping any antimalarial treatment at home, with only two (0.5%) doing so in Kwazulu Natal and five (1.2%) in Mpumalanga. Both of the households in Kwazulu Natal had AL at home, while in Mpumalanga two had chloroquine, one had doxycycline and two had quinine. These findings are reassuring as they suggest a high level of adherence with treatment.

Finally, 95% and 85% of household members who had suffered from malaria in the past 4 weeks in Kwazulu Natal and Mpumalanga respectively claimed not to have any medicines remaining from this treatment course. This correlated well with the 95.4% and 86.6% in Kwazulu Natal and Mpumalanga, respectively claiming to have completed all their medication. With one exception, the remainder of responses was 'unsure' and did not state that medicine was remaining or that they had not completed their treatment. Should these "unsure" responses indicate poor adherence, one would have expected the same households to report that they had malaria treatment at home, yet these were only 0.5% and 1.3% respectively. However, sharing of medicines with family and neighbours as described in the focus group discussions (SEACAT Annual Report, 2005) may also contribute to this discrepancy.

Overall, considering all four measures of adherence used in the household survey, and the findings of the focus group discussions (reported in the SEACAT 2005 Annual Report), it appears that a high level of adherence with treatment is being achieved in both provinces. Given the 3 day first line malaria treatment course in Kwazulu Natal, compared with the single SP dose in Mpumalanga, a higher level of adherence had been expected in Mpumalanga. The unexpected finding of poorer adherence in Mpumalanga deserves further investigation. However, adherence could not be

correlated with treatment used. The decades of successful malaria control in Mpumalanga may have resulted in these communities becoming complacent about the need to complete treatment, compared to the alarming malaria epidemic in Kwazulu Natal that may have motivated better adherence. Thirteen and 131 deaths attributed to malaria had occurred in the households surveyed in Mpumalanga and Kwazulu Natal, respectively.

Those household members who have ever had malaria reported taking malaria treatment for an average of 2.6 days in Mpumalanga and 2.4 days in Kwazulu Natal. Since some of these patients are likely to have been prescribed SP monotherapy, which is prescribed as a single stat dose, this data cannot be used to estimate likely adherence with a 3-day ACT treatment course. It was not possible to exclude these patients from the analysis, as the treatment administered was unknown for 67% and 30% of patients in Kwazulu Natal and Mpumalanga respectively. The validity of these answers are further limited by probable recall bias, as 86% and 30% of these episodes had occurred more than 4 weeks before and 5% and 14% had occurred before 2000 in Kwazulu Natal and Mpumalanga respectively. Thirteen and 131 deaths attributed to malaria had occurred in the households surveyed in Mpumalanga and Kwazulu Natal, respectively.

To describe the probable treatment seeking and adherence in those household members who did not recognise or recall that they have ever had malaria, household heads were also questioned regarding recent fever. Although none reported home use of any antimalarial for the treatment of recent fever in Mpumalanga, it is of concern that 57% of household members were reported to have attempted home treatment with chloroquine in Kwazulu Natal. Interestingly none of the households in Kwazulu Natal reported keeping chloroquine at home for the treatment of malaria, which suggests that chloroquine is no longer perceived by this community as a malaria treatment, but merely an antipyretic. Given the high levels of chloroquine resistance and the non-immune status of patients in South Africa, fevers due to malaria are not expected to have resolved with home treatment. Public clinics were the source of treatment in 93% and 64% of those who go on to seek treatment for recent fever in Kwazulu Natal and Mpumalanga, respectively. A considerably higher proportion of household members sought treatment at a private doctor for recent fever (27%) than recent malaria in Mpumalanga. This is consistent with findings in the focus group discussions that the public clinics are perceived to be a reliable source of antimalarial treatment, but regular stock outs of other medicines including

paracetamol result in patients purchasing antipyretic treatment from the supermarket or visiting private practitioners. Drug supply systems in Mpumalanga need to be critically re-evaluated and barriers to reliable drug supply urgently addressed.

Traditional healers were not a frequent source of treatment for malaria or fever. This is encouraging as the benefits of a change in malaria treatment to ACTs depend on high coverage, which would not be achievable if the majority of patients first sought treatment from a traditional healer. The "western" nature of the survey context and questions may bias household heads against reporting seeking treatment from traditional healers. However, the household survey findings are consistent with those of the focus group discussions (designed to minimize such bias)[16] that traditional healers are perceived as a source of care for other illness, but cannot provide effective treatment for malaria.

5.3.2: Changes in malaria health outcomes in Kwazulu Natal & Mpumalanga: baseline vs. Post-ACT

At baseline, malaria outpatients made up a relatively big proportion (13.8% and 7.1%) of the total outpatients seen at Kwazulu Natal clinics and hospital level respectively (Table 4.8), compared to only 1.24% and 2.96% in Mpumalanga (Table 5.2). This is consistent with difference in malaria incidence between the 2 study sites. In comparison, in the post-intervention phase, malaria outpatients made up a much smaller proportion of total outpatients in both Kwazulu Natal (0.62% at clinics and 0.66% at hospital) and Mpumalanga (0.32% at clinics and 0.75% at the two hospitals). Similarly, malaria admissions made up relatively higher proportions at baseline, 25.4% and 16.2%, of total admissions in Kwazulu Natal and Mpumalanga respectively, compared to 2.9% and 2.04% respectively at post-intervention (Tables 4.8 and 5.2).

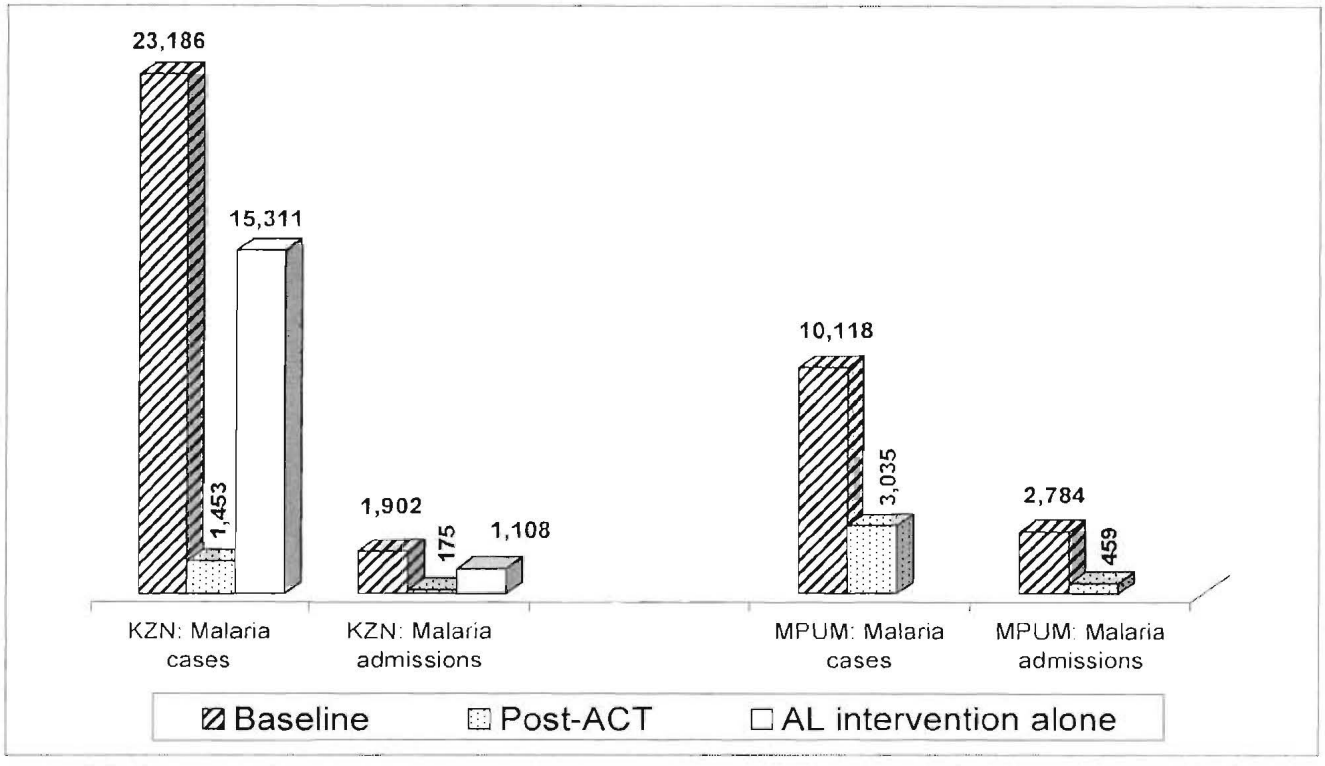
[16] Focus group discussions were conducted by other researchers on the SSECAT Evaluation.

Table 5.2: Change in malaria health outcomes (based on data from health facilities in 2 districts – Tonga and Shongwe) – in Mpumalanga

	32 Clinics (Baseline) 2000	32 Clinics (Post-ACT) 2003	% change	2 Hospitals (Baseline) 2000	2 Hospitals (Post-ACT) 2003	% change
Malaria outpatient cases	8,058	2,556	*-68.3%*	2,060	479	*-76.7%*
Total Headcounts	650,156	806,256	*24.0%*	69,605	63,681	*-8.5%*
Malaria as % of total headcounts	1.24%	0.32%		2.96%	0.75%	
Malaria Inpatient-days				19,488	2,517	*-87.1%*
Total hospital inpatient-days				88,599	370,207	*317.8%*
Malaria admissions				2,784	459	*-83.5%*
Total hospital admissions				17,173	22,471	*30.8%*

Results presented in Figure 5.2 show that the introduction of AS+SP as the first line drug for treating malaria in Mpumalanga has resulted in substantive reductions in both malaria cases and admissions. Similar results were achieved in Kwazulu Natal albeit the reductions in malaria cases and admissions are greater in Kwazulu Natal. The three key reasons for the differences in reduction in malaria cases and admission between Kwazulu Natal and Mpumalanga are: firstly, the far greater difference in efficacy between SP and ACT in Kwazulu Natal (AL 99% vs. 12% SP) than Mpumalanga (AS+SP 99% vs. SP 90%); secondly evaluations of change in treatment policies were undertaken 2 years after the new treatment policy was in place in Kwazulu Natal and only after one year after the new treatment policy was in place in Mpumalanga; and lastly, synergistic impact of the 3 interventions (re-introduction of IRS with DDT, introduction of IRS in Southern Mozambique, and change to artemether-lumefantrine as first line treatment for malaria) has resulted in greater reductions in Kwazulu Natal compared to Mpumalanga where only one intervention (change to AS+SP as first line treatment) was implemented.

Figure 5.3: Comparing malaria cases and admissions at baseline and post-intervention in Kwazulu Natal and Mpumalanga.



Source: Data from the sampled health facilities (clinics and hospitals) in Kwazulu Natal and Mpumalanga

Table 5.3 and Figure 5.3 provide a more precise picture of the changes in malaria morbidity before and after the introduction of changes in malaria control initiatives (including the use of ACTs as first line drugs) in Kwazulu Natal and Mpumalanga. In the absence of the other interventions, it is estimated that the introduction of artemether-lumefantrine as first line drug in Kwazulu Natal would have resulted in a 34% reduction in malaria cases and a 42% reduction in malaria admissions, based on the Delphi survey results (See Section 4.3.2). These reductions in malaria cases and admissions are much lower than those that were actually observed for the same period (94% for malaria cases and 91% for malaria admissions) attributed to all interventions implemented in Kwazulu Natal. From the results presented in Table 5.3, it is clear that the use of AS+SP in Mpumalanga had an impact on malaria disease burden (70% and 83.5% reduction in malaria cases and admissions respectively) that is clearly better than the estimated impact of artemether-lumefantrine alone in Kwazulu Natal (34% and 42%). Even when one considers the upper limit of the Delphi estimates of impact of artemether-lumefantrine (50% and 60% reduction in cases and admissions, respectively), the one-year impact of AS+SP on malaria outcomes in Mpumalanga remains higher than the estimated two-year impact of

artemether-lumefantrine in Kwazulu Natal. This suggests that the Delphi estimates of the contribution of artemether-lumefantrine to the improvement in malaria health outcomes might have been very conservative.

Table 5.3: Comparing malaria health outcomes pre- and post-ACT in Kwazulu Natal and Mpumalanga (data from sample of health facilities, except for notified deaths which are for the whole province)

	Year	*2000*	*KZN: 2002; ACT evaluated after 2 years MPUM: 2003; ACT evaluated after 1 year*		
		Baseline	**Post-intervention**	**observed % change**	**Contribution of ACT to decline**
Malaria outpatient cases *(at clinic & hospital OPD)*	Kwazulu Natal	23,186	1,453	*-93.7%*	*-34%*
	Mpumalanga	10,118	3,035	*-70.0%*	*-70%*
Malaria Admissions	Kwazulu Natal	1,902	175	*-90.8%*	*-42%*
	Mpumalanga	2,784	459	*-83.5%*	*-83.5%*
Malaria deaths (whole province)	Kwazulu Natal	340	16	*-95.3%*	*-60%*
	Mpumalanga	45	34	*-24.4%*	*-24.4%*

Source: Hospital and Clinics records in Kwazulu Natal and Mpumalanga.

An interesting finding in Table 5.3 is that while Kwazulu Natal has more than double the outpatient malaria cases than Mpumalanga, Mpumalanga had a higher number of malaria admissions than Kwazulu Natal, particularly at baseline. At baseline, the malaria outpatient to malaria admissions ratios for Kwazulu Natal and Mpumalanga are 12.2 and 3.6, respectively, and at post-intervention the ratios are 8.3 and 6.6 respectively. Clearly, Mpumalanga was treating more malaria patients as inpatients rather than as outpatients. As noted earlier, this is explained by Mpumalanga's more conservative admission policy, which encouraged the admission of uncomplicated malaria cases who were considered "at increased risk" in any way- particularly high risk groups (all young children and pregnant women) and those recently treated for malaria. As a result of this policy, particularly that admitting any patient treated for malaria in the past month or two, it is not surprising that although the greatest impact of ACTs is expected to be at outpatient level, use of AS+SP is found to have resulted in a higher reduction in malaria admissions (83.5%) than in malaria outpatients (70%) in Mpumalanga, while the reverse is true for Kwazulu Natal (**90.8%** reduction in malaria admissions and

93.7% in malaria outpatients at both clinic and hospital OPD). This is possible because with improved cure rates (and decreased gametocyte carriage) with AS+SP, Mpumalanga had fewer "recently treated" uncomplicated cases to admit. However, the lower ratio of malaria outpatients to admissions in Mpumalanga (6.6) compared to Kwazulu Natal (8.3), at the post-intervention phase, indicates that Mpumalanga remained relatively conservative with their admission policy and practices even after the implementation of an ACT as the first line drug. Alternatively, the populations in Mpumalanga might have been slightly more prone to developing severe malaria at the post-intervention phase compared to those in Kwazulu Natal where malaria prevalence had been higher than in Mpumalanga. Even at the intensities of malaria transmission in Kwazulu Natal which were relatively low in comparison to most of Africa, there appears to be some level of acquired immunity [180].

Table 5.3 also shows that at baseline there were more malaria-related deaths in Kwazulu Natal compared to Mpumalanga, mainly because despite SP being ineffective in Kwazulu Natal a larger proportion of uncomplicated malaria cases were treated with SP and chloroquine than in Mpumalanga, where many uncomplicated malaria cases were hospitalised and treated as inpatients (with Quinine). It is interesting to note that even with the higher admission rates for malaria patients in Mpumalanga, compared to Kwazulu Natal, there was a relatively small decline (24.4%) in the number of deaths in Mpumalanga between the baseline and post-intervention phases (Table 5.3). This is likely to be due to the fact that SP was still highly effective in Mpumalanga at the time of changing treatment policy, hence the impact of the change to AS+SP in Mpumalanga on malaria mortality is relatively lower than that of the change to artemether-lumefantrine in Kwazulu Natal where SP was highly ineffective.

The impact of an ineffective first line antimalarial on malaria-related mortality is confirmed by the differences in the case fatality ratios and the death to admissions ratios in the two study sites. Table 5.3 shows that Kwazulu Natal province (where SP was more ineffective) had a higher ratio of malaria-related deaths to admissions (18%) compared to Mpumalanga (2%) at baseline. However, post-intervention, where artemether-lumefantrine and AS+SP are both very effective, these ratios for Kwazulu Natal (9%) and Mpumalanga (7%) were similar. However, this study is not able to reliably evaluate case fatality ratios as the number of deaths have been collected for the whole province so cannot be related to the number of malaria cases only in the study site.

5.3.3: Changes in costs and unit costs: Baseline vs. Post - ACT intervention

This section presents and discusses the costs and unit costs related to the introduction of ACTs as first line drugs for malaria treatment in Mpumalanga and compares these costs with those in Kwazulu Natal. While the costs related to the implementation of this policy in both provinces are described, findings focus on costs and unit costs related to the management of malaria patients following the introduction of ACTs.

5.3.3.1: Comparing cost of implementing ACT policy in Kwazulu Natal & Mpumalanga

In Mpumalanga, a change in malaria first-line drug was guided by the results of the in-vivo studies which showed that although there was a low trend towards decreasing efficacy of SP monotherapy in treating uncomplicated malaria, there was a highly significant increase in gametocyte carriage [162]. Following this finding, policy meetings and discussions were held between malaria and public health experts, the Malaria Control Program officials in Mpumalanga, academics and the Malaria Advisory Group of South Africa. These discussions reached consensus to change first line treatment to an ACT, artesunate+SP. A one day workshop, organised to launch the new drug (Arsudar®) and provide training on its safe and effective use, was attended by directors in the Provincial and National Departments of Health, Public sector doctors, pharmacists and nurses. A separate training workshop was held with the private GPs in malaria transmission areas of Mpumalanga.

As in the case of Kwazulu Natal, the estimation of cost of implementation of the new policy was difficult because most activities relating to the change of treatment policy were undertaken by the Provincial Department of Health and Malaria Control Program as part of their routine work. The activities mainly included meetings to discuss new policy options and to choose the best option for Mpumalanga, printing of treatment guidelines, training of health workers on the new treatment policy, withdrawal of SP from and the distribution of AS+SP (Arsudar®) to health facilities and routine supervision and monitoring. Implementation of the policy did not require additional staff, so no additional personnel costs were incurred.

The costs incurred in implementing the new treatment policy in Mpumalanga (US$ 8,323) are comparable to those incurred in Kwazulu Natal (US$ 7,580). The reason for this is because both provinces have a fairly well-developed health infrastructure and well established Malaria Control Programs that undertook this implementation. The implementation costs reported for both provinces cannot be generalised for other settings in sub-Saharan Africa, where health systems and infrastructure are not adequately funded and where Malaria Control Programs lack the capacity to undertake such activities as part of routine work. In addition, successful implementation of such a policy change is likely to be more challenging and to require a sizeable amount of resources in areas where malaria is prevalent in the entire country as opposed to a small area (e.g. region or province).

5.3.3.2: Comparing changes in costs of managing uncomplicated malaria in Kwazulu Natal & Mpumalanga

With the introduction of AS+SP (a relatively more expensive drug than its predecessor – SP monotherapy) and the reductions in number of malaria cases and admissions shown in Figure 5.3 we expect changes in the costs of managing malaria patients in Mpumalanga. Table 5.4 provides a comparative analysis of the costs of treating malaria outpatients at clinic and hospital levels in Mpumalanga, before and after the change to AS+SP as first line drug. The findings in Table 5.4 reveal that there were substantive reductions in the cost of treating malaria patients, both at clinic and hospital outpatient levels, after the introduction of AS+SP. In spite of the fact that AS+SP is a more expensive drug than SP monotherapy, there are substantive reductions in the cost of antimalarials for malaria outpatients (i.e. 72% and 90.9% reduction at clinic and hospital levels, respectively). Furthermore, there were substantive reductions in 'other malaria-related recurrent costs' (74%) and capital costs (84%), at both clinic and hospital levels, between the baseline and post-intervention phases in Mpumalanga. The only cost item where reduction in costs is not substantive is that of diagnostic costs. This is true because since non-malaria fevers made up a big proportion (68%) of the total fever cases at baseline, and are likely not to change significantly in the short term (one year), they are likely to keep the total number of fever cases (hence number of cases to be tested) high even when the actual number of malaria cases declines. Particularly, in the short term, health workers are likely to continue suspecting malaria in many fever patients and thus test them to exclude malaria.

Overall, a 66.3% reduction in total costs related to managing uncomplicated malaria (outpatients) at clinic and hospital was achieved in Mpumalanga (Table 5.4). This translated into cost savings of US $24,276 resulting from the health facilities (32 clinics and 2 hospitals) included in the study (i.e. in 2 districts). This means that use of ACTs in Mpumalanga has the potential for greater cost-savings if the entire province is taken into consideration. These findings are similar to the ones reported in chapter 4 (for the economic evaluation of artemether-lumefantrine in Kwazulu Natal) and confirm our earlier conclusion that in spite of being more expensive than traditional monotherapy antimalarials, ACTs can be cost-saving in some contexts.

Table 5.4: Changes in malaria outpatient costs in Mpumalanga: baseline vs. post-ACT; based on findings from a sample of health facilities in 2 districts in Mpumalanga

Outpatient Costs (US $) 2002 prices	**32 Clinics (baseline)**	**32 Clinics (Post- ACT)**	**observed % change**	**2 Hospitals (baseline)**	**2 Hospitals (Post-ACT)**	**observed % change**
Antimalarial costs	15,423	4,323	*-72.0%*	8,937	810	*-90.9%*
Cost of Malaria tests	20,050	15,738	*-21.5%*	2,956	2,219	*-24.9%*
Other recurrent Exp	20,068	5,132	*-74.4%*	31,098	4,971	*-84.0%*
Capital expenditure	2,260	578	*-74.4%*	3,478	1,325	*-84.0%*
TOTAL malaria expenditure	**57,801**	**25,771**	*-55.4%*	**46,469**	**9,325**	*-79.9%*
Cost Savings		**$15,412**			**$8,864**	
Mpumalanga: % total reduction in malaria outpatient costs: baseline vs. ACT						**66.3%**
KZN: % total reduction in malaria outpatient costs attributable to artemether-lumefantrine: baseline vs. ACT						**31.8%**

By comparison, an 88.9% reduction in total costs of managing malaria outpatients in Kwazulu Natal was realised as a result of the 3 interventions. In the absence of other interventions, it is estimated that the use of artemether-lumefantrine as first line drug would have resulted in a 31.8% reduction in total malaria outpatient costs, which is considerably lower than the percentage reduction for AS+SP (66.3%) in Mpumalanga. This finding confirms the initial suggestion that the Delphi estimates of the impact artemether-lumefantrine in Kwazulu Natal might have been rather conservative. The overall reduction in total malaria outpatient costs in Kwazulu Natal translates into cost-savings of US$47,342.

Interestingly, despite this lower percentage reduction, relatively higher cost savings were realised in Kwazulu Natal (US$ 47,342) than in Mpumalanga (US$ 24,276), moreover the health facilities included in the study in Mpumalanga are more than those in Kwazulu Natal. The explanation for this lies in the fact that total malaria outpatient costs at baseline in Kwazulu Natal (US$ 230,783) is 2.2 times higher than the baseline outpatient malaria costs in Mpumalanga (US$104,270), due to the higher number of malaria cases in Kwazulu Natal at baseline (which is 2.3 times higher than that of Mpumalanga at baseline).

Table 5.5 shows that the unit costs of treating malaria outpatients at baseline in Kwazulu Natal ($7.62 and $24.21 at clinic and hospital level, respectively) are not substantially different from those for Mpumalanga ($7.17 and $22.56 at clinic and hospital level, respectively). The slight difference in baseline unit costs (i.e. *cost per malaria outpatient treated*) between Kwazulu Natal and Mpumalanga is possibly explained by the higher personnel costs in Kwazulu Natal compared to Mpumalanga. For example at clinic and hospital levels, at baseline, *personnel cost per malaria patient treated* is $3.47 and $17.99 in Kwazulu Natal compared to $2.29 and $13.92 in Mpumalanga, respectively. In fact, for the post-intervention phase, *personnel cost per malaria patient treated* is considerably higher in Kwazulu Natal ($2.68 and $18.96 at clinic and hospital level, respectively) compared to that for Mpumalanga ($1.85 and $8.71), which explains the considerable differences in **cost per malaria outpatient treated**, at post-intervention phase, for Kwazulu Natal ($14.61 and $30.08) and Mpumalanga ($10.08 and $19.47) at clinic and hospital respectively (see Table 5.5). Interestingly, however, Kwazulu Natal had a lower *nurse to malaria patient* ratio (0.08) than Mpumalanga (0.14), at hospital level.

Table 5.5 provides a summary of the unit costs at different levels of care in Kwazulu Natal and Mpumalanga, at baseline and post-intervention. The unit costs presented in Table 5.5 for the post-intervention phase, for Kwazulu Natal, capture the total effect of the impact of the 3 interventions (see detailed description of these in chapter 4). From a general point of view, at both baseline and post-ACT phases, Mpumalanga spent slightly less than Kwazulu Natal on every malaria outpatient treated. That is, ***cost per malaria outpatient*** (calculated on total costs, including other recurrent and capital costs) for Mpumalanga was consistently lower than that for Kwazulu Natal at both clinic and hospital levels. However, at baseline, *cost per malaria outpatient* (calculated on costs of antimalarial and

diagnostic alone) was slightly lower in Kwazulu Natal compared to Mpumalanga, and vice versa for the post-intervention phase. These findings mean that at both clinic and hospital levels, at baseline and post-ACT phases, Kwazulu Natal was spending more on "other recurrent and capital" costs per malaria outpatient. As discussed previously, one item where Kwazulu Natal was spending much more than Mpumalanga is that of personnel.

Despite having the same official treatment policy at baseline (i.e. SP monotherapy) in both Kwazulu Natal and Mpumalanga, the *antimalarial cost per malaria outpatient treated* is different in the two provinces due to different practices in managing uncomplicated malaria in the face of drug resistance associated with SP monotherapy. In practice, Kwazulu Natal routinely treated patients with uncomplicated with SP and chloroquine while Mpumalanga treated them with SP (but often added quinine). These differences help explain the higher *antimalarial cost per malaria outpatient* in Mpumalanga ($1.91 and $4.34) compared to that in Kwazulu Natal ($1.27 and $1.31), at clinic and hospital OPD levels respectively, at baseline, given that quinine is more expensive than chloroquine. Not surprisingly, for the post-intervention phase, the *antimalarial cost per malaria outpatient* is higher in Kwazulu Natal ($2.85) compared to Mpumalanga ($1.69) because artemether-lumefantrine is more expensive (used in Kwazulu Natal) than AS+SP (used in Mpumalanga). The frequent use of quinine at baseline also explains the unexpected finding that more was spent on antimalarials when SP was official policy, than post intervention when artesunate plus SP was official policy.

Table 5.5: Changes in unit costs for malaria outpatients: baseline vs. post-ACT; based on findings from a sample of health facilities in 1 and 2 districts in Kwazulu Natal & Mpumalanga respectively

	KWAZULU NATAL				MPUMALANGA			
Outpatient Costs (US $) 2002 prices	9 Clinics: baseline	9 Clinics: Post-intervention	1 Hospital: baseline	1 Hospital Post: intervention	32 Clinics: baseline	32 Clinics: Post-ACT	2 Hospitals: baseline	2 Hospitals: Post-ACT
malaria cases	19,925	1,166	3,261	287	8,058	2,556	2,060	479
Cost per malaria outpatient (total malaria costs)	$7.62	$14.61	$24.21	$30.08	$7.17	$10.08	$22.56	$19.47
Antimalarial cost per outpatient treated	$1.27	$2.85	$1.31	$2.85	$1.91	$1.69	$4.34	$1.69
Diagnostic cost per malaria outpatient treated	$1.49	$8.00	$0.85	$3.99	$2.49	$6.16	$1.43	$4.63

Results presented in Table 5.5 demonstrate that, at clinic level (baseline), Mpumalanga spent 1.6 times ($4.4) more than Kwazulu Natal ($2.8) on antimalarials and diagnostic tests per malaria outpatient treated. At the clinic level, at baseline, while both Kwazulu Natal and Mpumalanga spent nearly the same amount of money on antimalarials per outpatient ($1.27 and $1.91, respectively), Mpumalanga spent considerably more ($2.49) on diagnostics on each malaria patient treated than Kwazulu Natal ($1.49) at that level. This might possibly be because Mpumalanga tested a relatively larger number of people, but only a small proportion was found positive. Furthermore, Table 5.5 shows that at hospital level, at baseline, Mpumalanga spent 2.7 times more ($5.77) than Kwazulu Natal ($2.16) on antimalarials and diagnostics for every malaria outpatient treated. Although, official first line treatment for malaria and diagnostic approaches were the same in both provinces at baseline, actual treatment practice varied from health facility to health facility especially in light of the high treatment failures associated with SP monotherapy. In addition, although second line treatment policy (for malaria inpatient cases) was the same in both provinces, the admission policies and practices were different, as previously discussed.

5.3.3.3: Comparing changes in malaria inpatient costs and unit costs

Table 5.6 presents a comparative analysis of the costs of treating malaria at inpatient level in Mpumalanga before and after introducing AS+SP. Although AS+SP is used for treating uncomplicated malaria, its use as first line drug is expected to have a positive impact on severe

malaria particularly in the context where its predecessor is a less effective drug (SP monotherapy). Table 5.3 reveals an 83.5% reduction in number of malaria admissions in Mpumalanga, which could be attributed to the change to AS+SP[17], since there were no changes in the management of severe malaria (malaria inpatients). Table 5.6 shows a 70.8% reduction in cost of drugs for malaria inpatients, which is mainly due to a sizeable reduction in the number of malaria inpatient cases (i.e. malaria admissions) needing treatment. Furthermore, the 83.5% reduction in malaria admissions in Mpumalanga (Table 5.3) results in considerable reductions in capital and other costs (see Table 5.6), although these do not translate into financial cost-savings. Overall, an enormous reduction (93%) in total malaria inpatient costs is realised. However, this translates into cost savings (on antimalarial and diagnosis costs) of US$ 7,053 (at inpatient level) in Mpumalanga (Table 5.6).

Table 5.6: Comparing changes in inpatient malaria costs in Mpumalanga: baseline vs. post-ACT; based on data from 2 district hospitals only.

Inpatient Costs (US $) 2002 prices	2 Hospitals: baseline	2 Hospitals: post-intervention	% *Reduction*
Antimalarial costs	7,099	2,074	*70.8%*
Cost of Malaria tests	2,634	606	*77.0%*
Other recurrent Exp	939,072	58,838	*93.7%*
Capital expenditure	164,477	16,624	*89.9%*
TOTAL malaria costs	**$ 1,113,283**	**$ 78,142**	*93.0%*
Cost Savings (US $)		$ 7,053	

MPUM: % total reduction in malaria inpatient costs: baseline vs. ACT	93%
KZN: % total reduction in malaria inpatient costs attributable to AL: baseline vs. ACT	41%
KZN: % total reduction in malaria inpatient costs: baseline vs. all 3 interventions	89.3%

By comparison, Kwazulu Natal realised an 89.3% reduction in total malaria inpatient costs, resulting in a cost-saving of US$ 9,028 in the studied hospital (Manguzi hospital) (Table 4.12). Note that the difference in cost-savings, at inpatient level, between Kwazulu Natal ($ 9,028) and Mpumalanga ($7,053) are not substantively different.

[17] Although other factors could contribute to reduction in severe malaria, it is unlikely that these factors could be responsible for such a marked decline in malaria admissions in a relatively short period of time that has been considered for this study.

Table 5.7: Comparing changes in unit costs for malaria inpatients in Kwazulu Natal and Mpumalanga: baseline vs. post-ACT; based on data from 1 and 2 district hospitals, respectively.

	KWAZULU NATAL			MPUMALANGA	
Inpatient Unit Costs (US $) 2002 prices	1 Hospital: baseline	1 Hospital: post-intervention	Attributable to AL (based on Delphi results)	2 Hospitals: baseline	2 Hospitals: post-intervention
No. of admitted patients	1,902	175	1,108	2,784	459
No. of in-patient days	13,314	1,225	7,753	19,488	2,517
ALOS	7	7	7	7	5
cost per malaria inpatient day (*total costs*)	$24.99	$29.03	$25.30	$57.13	$31.05
Antimalarials cost per inpatient-day	$0.54	$0.74	$0.74	$0.36	$0.82
diagnostic cost per inpatient-day	$0.36	$1.71	$0.34	$0.14	$0.24

Table 5.7 presents a comparison of the unit costs for malaria inpatient services in Kwazulu Natal and Mpumalanga, at baseline and after the change to ACTs. Findings in Table 5.7 reveal that on average, Mpumalanga spent 2.3 times more per malaria inpatient-day than Kwazulu Natal at baseline. However, for the post-intervention phase, nearly the same amount was spent per malaria inpatient-day in Kwazulu Natal ($29.03) and Mpumalanga ($31.05). Interestingly, although *antimalarial cost per inpatient-day* is not radically different in Mpumalanga and Kwazulu Natal, at both baseline and post-intervention phases, Kwazulu Natal spent reasonably more on diagnostics for every inpatient-day than Mpumalanga, both at baseline and post-ACT, because they did more diagnostic tests than Mpumalanga. For example at baseline, 2.1 rapid tests and 0.97 microscopy tests were done per malaria outpatient and malaria admission, respectively, in Kwazulu Natal compared to 1.8 and 0.84 in Mpumalanga. For the post-ACT phase, Kwazulu Natal did 12.3 rapid tests per malaria outpatient and 2.2 microscopy test per malaria admission, compared to 5.8 and 1.2, respectively, in Mpumalanga. This is possibly due to the fact that Kwazulu Natal had more febrile cases than Mpumalanga. Also, as Kwazulu Natal has had a greater burden of malaria than Mpumalanga historically, clinicians are likely to continue testing for malaria extensively, during the post-ACT phase, despite the massive reduction on the malaria burden. Diagnostic costs presented include the costs of diagnostics for all febrile

(fever) cases (i.e. include the diagnostic costs for febrile patients who end up being malaria negative), but the unit cost presented in Table 5.7 are expressed as *total malaria diagnostic costs per malaria positive patient (i.e. per confirmed malaria case)*. Note that all febrile (fever) cases are 'suspected' to be malaria cases (hence all are tested) and the 'actual' malaria cases become the confirmed cases (i.e. those who turn out to be positive). Also, Table 5.7 reveals that average length of stay (ALOS) dropped from 7 to 5 in Mpumalanga, between baseline and post-intervention phases, while it remained the same in Kwazulu Natal. Such changes have contributed to the differences in levels of costs savings realised in the 2 study sites.

5.3.4: Comparing the cost-effectiveness of AL (Kwazulu Natal) & AS+SP (Mpumalanga)

The cost-effectiveness analysis sets out to calculate *incremental cost per malaria patient treated* for AL and artesunate+SP. In both the Kwazulu Natal and Mpumalanga studies, the ICER measures the **incremental cost / cost-saving per malaria case averted or malaria inpatient-day averted**. In the analysis, the incremental cost-effectiveness ratio has been calculated as:

ICER = (Intervention costs – Baseline costs) / (Intervention health outcomes – Baseline health outcomes)

For all the scenarios in Kwazulu Natal and Mpumalanga, there are cost-savings (and not additional costs) as well as improved health outcome, hence giving us negative values for both incremental costs and outcomes, and positive incremental cost-effectiveness ratios.

Table 5.8 provides a comparative analysis of the incremental and average cost-effectiveness ratios associated with the change from SP (baseline) to ACTs in Kwazulu Natal and Mpumalanga. Findings presented in Table 5.8 show that there are cost savings associated with ACTs at both outpatient and inpatient levels for both Kwazulu Natal and Mpumalanga. For outpatient level, the average cost effectiveness ratio for SP and AL (in Kwazulu Natal) is $9.95 and $17.67, respectively (see Table 4.14), compared to that of SP and AS+SP (in Mpumalanga) of $10.31 and $11.56, respectively.

Table 5.8: Comparing ACER and ICER for AL (Kwazulu Natal) and AS+SP (Mpumalanga)

BASELINE (Treat with SP for Outpatients and with Quinine [5-7days] for inpatients)				
		Total Cost (2002 US $)	Cases or inpatient-days	Unit cost (2002 US $)
KZN	Malaria outpatient services	230,783	23,186	9.95
	Malaria inpatient services	332,750	13,314	24.99
MPUM	Malaria outpatient services	104,270	10,118	10.31
	Malaria inpatient services	1,113,283	19,488	57.13

Post ACT (Treat with AL or AS+SP for Outpatients and with Quinine [5-7days] for inpatients)						
		Malaria outpatient cost	Number of cases	Average cost/malaria outpatient	Reduction in malaria costs (2002 US$)	ICER
KZN	Malaria outpatients (100% change)	25,670	1,453	17.67	205,114	$9.44
	Adjusted for 36% (median)	**157,440**	**15,362**	**10.25**	**73,343**	**$9.37**
Sensitivity analysis	Adjusted for 25% (lower range)	180,729	17,753	10.18	50,054	$9.21
	Adjusted for 50% (upper range)	127,450	12,320	10.35	103,334	$9.51
MPUM	Malaria outpatients	35,097	3,035	11.56	**69,173**	$9.77
		Malaria inpatient cost	No. of malaria inpatient days	Average cost/malaria inpatient-day	Reduction in malaria costs (2002 US$)	ICER
KZN	Malaria inpatient-days (100% change)	35,557	1,225	29.03	297,193	$24.58
	Adjusted for 46% (median)	**196,168**	**7,753**	**25.30**	**136,583**	$24.56
Sensitivity analysis	Adjusted for 35% (lower range)	225,917	9,083	24.87	106,834	$25.25
	Adjusted for 60% (upper range)	156,794	6,061	25.87	175,956	$24.26
MPUM	Malaria inpatient-days	78,142	2,517	31.05	**1,035,141**	$60.99

Note: For KZN, cases and costs have been calculated based on estimates of % contribution of AL to decline in malaria cases and admissions (obtained through a Delphi survey). Ranges have been used for sensitivity analyses.

Results in Table 5.8 also show that the *reduction in malaria costs per malaria outpatient case averted* of AL and AS+SP interventions is $9.44 ($9.21 - $9.51) and $9.77, respectively. Note that since these interventions result in both cost savings and improved health outcomes, then the ICER is interpreted as *'cost saving per malaria outpatient case averted'*. Since the use of ACTs results in cost-savings,

for both artemether-lumefantrine and AS+SP, then ACTs have been found to be more cost-effective than SP monotherapy. The insignificant difference between the ICER for malaria outpatients for artemether-lumefantrine and AS+SP shows that both ACTs are equally cost-effective. Although the average ***cost per malaria inpatient-day*** associated with the use of artemether-lumefantrine in Kwazulu Natal ($29.03) and AS+SP in Mpumalanga ($31.05) are not substantially different, there is a considerable difference between the ICER for malaria inpatients (i.e. *reduction in cost per malaria inpatient-day averted*) for artemether-lumefantrine ($24.58) in Kwazulu Natal and that for AS+SP ($60.99) in Mpumalanga (see Table 5.8). This means that when the overall cost-effectiveness of these drugs is considered, that is to take into account their impact on all malaria health outcomes (uncomplicated malaria cases, severe/inpatient malaria cases and deaths), then AS+SP is likely to be more cost-effective than artemether-lumefantrine. However, it is difficult to arrive at such a conclusion without explicitly calculating it. Moreover, it is also important to note that the overall cost-effectiveness of the two drugs could be heavily influenced by changes in clinical practice in Mpumalanga (i.e. lower admissions and lower *average length of stay for malaria patients* in the post-intervention phase) and also by different cost structures in the two provinces (with Kwazulu Natal having relatively higher personnel and capital costs). The use of economic models helps one to undertake such comprehensive evaluations of interventions. In this specific study, results of the decision tree models (presented and discussed section 5.3.5) show that indeed AS+SP is relatively more cost-effective than artemether-lumefantrine.

Table 5.9 presents a summary of the sensitivity analyses results for Mpumalanga. Mpumalanga spent ZAR 5.40 (=US$ 0.77) while Kwazulu Natal spent ZAR 16.07 (US$ 2.29) on a dose of SP in 2000. Results show that if Mpumalanga had purchased SP at the price that Kwazulu Natal purchased in 2000, there would have been significant changes in the results. For example, the *cost per malaria outpatient* with the higher SP prices would be US$ 14.63, compared to US$ 10.31 which is the unit cost in Mpumalanga at baseline. However, sensitivity analyses results show that even when the annualisation rates are varied and higher price of SP are considered, the change from SP monotherapy to AS+SP still results in considerable cost savings at the outpatient level.

Table 5.9: One-way and Multi-way sensitivity analysis results for Mpumalanga (price of SP, annualisation rates; average length of inpatient stay)

	Lowest estimates	Highest estimates
Cost per malaria outpatient	$14.63	$14.85
Variable assumptions	3% annualisation rate for capital; Higher prices of SP as those used for Kwazulu Natal	8% annualisation rate for capital; Higher prices of SP as those used for Kwazulu Natal
Cost saving on outpatient care	$112,893	$115,155
Variable assumptions	3% annualisation rate for capital; Higher prices of SP as those used for Kwazulu Natal	8% annualisation rate for capital; Higher prices of SP as those used for Kwazulu Natal
Inpatient-day unit cost	$31.12	$31.36
Variable assumptions	3% annualisation rate for capital; 3 days average length of stay	8% annualisation rate for capital; 7 days average length of stay
Cost saving on inpatient care	$1, 034,349	$1,034,953
Variable assumptions	8% annualisation rate for capital; 7 days average length of stay	3% annualisation rate for capital; 3 days average length of stay

5.3.5: Cost-effectiveness of AS+SP using Decision Tree Model for Mpumalanga study site

As in the case of Kwazulu Natal, a decision tree model was used to evaluate the overall cost-effectiveness of first line antimalarial drugs, combining the costs and health outcomes associated with management of both uncomplicated and severe malaria. To allow for direct comparison of the results from the decision tree models, the same type of model was used for Kwazulu Natal and Mpumalanga (Figures 4.5 and 5.4), but the variables were assigned different sensitivity analysis values relevant for the study sites (Tables 4.18 and 5.11). The definitions and values of the variables used in the Kwazulu Natal and Mpumalanga models are presented in chapter 3 (Table 3.6). The results of the Kwazulu Natal model are presented and discussed in chapter 4.

Results of the Mpumalanga decision tree model reveal that the option to treat with AS+SP has a lower cost-effectiveness ratio than the SP monotherapy option. This finding that AS+SP is more cost-effective than SP monotherapy confirms the results presented and discussed earlier (Table 5.8), where it has been shown that relative to the SP monotherapy alternative, the AS+SP alternative results in cost-savings as well as improved health outcomes. Hence, the SP monotherapy option is 'dominated' by the AS+SP option as was the case for artemether-lumefantrine in Kwazulu Natal.

Figure 5.4: Evaluation of the cost-effectiveness of first line antimalarials in Mpumalanga using a decision tree model

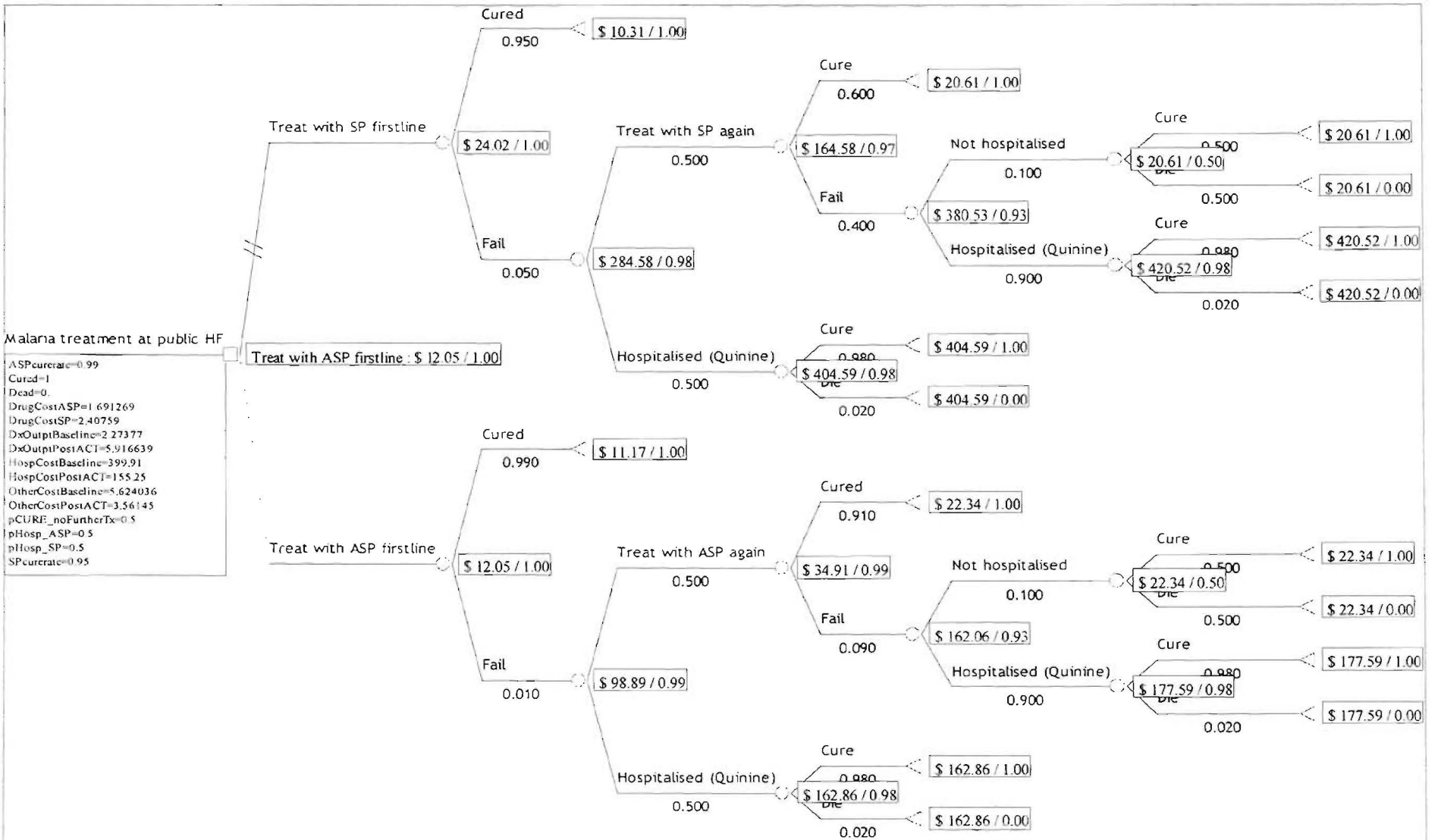


Table 5.10: Summary of cost-effectiveness results from the Mpumalanga decision tree model

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E
Treat with ASP firstline	$ 12.0		0.99987		$ 12.05	
Treat with SP firstline	$ 24.0	$ 12.0	0.99882	-0.00105	$ 24.05	(Dominated)
Dominance Report:						
The strategy "Treat with SP firstline" is dominated by "Treat with ASP firstline".						

Comparisons between the results of the decision tree models for Kwazulu Natal and Mpumalanga bring out important findings. Firstly, both models confirm that ACTs are more cost-effective than SP monotherapy. It is particularly interesting to see that ACTs are relatively more cost-effective (and cost-saving) even in the case of Mpumalanga where the effectiveness (cure rate) of SP monotherapy (95%)[18] is almost as high as that of AS+SP (99%). This clearly brings out a policy implication that even in the best circumstance where monotherapy drugs are still efficacious it is probably worthwhile to consider the use of ACTs for first line treatment.

Secondly, although the SP monotherapy option is dominated in both situations (i.e. artemether-lumefantrine and AS+SP options), the cost-effectiveness ratio of SP monotherapy in the case of Mpumalanga ($24.05) is significantly lower than that of SP monotherapy in Kwazulu Natal ($118.28). The most plausible explanation for this phenomenon mainly lies in the significantly different cure rates for SP monotherapy in Kwazulu Natal (12%) and Mpumalanga (95%). The fact that more people will fail treatment (with SP monotherapy) in Kwazulu Natal than in Mpumalanga implies that more people will require further treatment and hence attract more costs. In fact, the baseline unit costs of treating malaria patients were relatively higher in Mpumalanga ($10.3 and $399.91 for malaria outpatients and inpatient admissions, respectively) than in Kwazulu Natal ($9.95 and $174.93 for malaria outpatients and inpatient admissions, respectively), but the C/E ratio for SP monotherapy in Mpumalanga is only one-fifth of that in Kwazulu Natal. Since nothing else in the two models is different, the difference in SP cure rates is responsible for the differences in the C/E ratios in the two models.

[18] This cure rate for SP monotherapy was conservatively estimated (i.e. at the time when these analyses were done), but actually the literature shows that cure rate for SP monotherapy was 93% in 2000 and 90% in 2002.

Thirdly, results from the 2 models show that AS+SP (a relatively cheaper ACT) has a lower C/E ratio ($12.05) than artemether-lumefantrine ($18.81), which makes logical sense since both of them are considered to have the same effectiveness (with a cure rate of 99%). The extent to which one of the two ACTs would be more cost-effective (or cost-saving) than the other depends on the baseline contextual issues (i.e. the baseline antimalarial, its effectiveness and the costs associated with its use).

As in the case for Kwazulu Natal, sensitivity analyses have been done for the Mpumalanga decision tree model. The sensitivity analyses values used for each of the variable are presented in Table 5.11. In order to allow comparison of results from the Kwazulu Natal and Mpumalanga models, most of the lowest and highest values used for variables in the two models are the same (see Tables 4.19 and 5.11).

Table 5.11: Values used for sensitivity analysis in the Mpumalanga decision tree model

Variable	Value used in Mpumalanga tree	sensitivity analyses lowest value	sensitivity analyses highest value
ASPcurerate	0.99	0.12	0.99
SPcurerate	95	0.12	0.99
Cured	1	1	1
Dead / Die	0	0	0
DrugCostASP	$1.69	$1.00	$3.24
DrugCostSP	$2.41	$0.20	$2.41
DxOutptBaseline	$2.27	$0.50	$2.27
DxOutptPostACT	$5.92	$0.50	$7.21
HospCostBaseline	$399.91	171.39 (3 days)	399.91 (7 days)
HospCostPostACT	$155.25	93.15 (3 days)	217.35 (7 days)
OtherCostBaseline	$5.62	$0.00	$10.00
OtherCostPostACT	$3.56	$0.00	$10.00
pCURE_noFurtherTx	0.5	0.1	0.8
pHosp_ASP	0.5	0.1	0.8
pHosp_SP	0.5	0.1	0.8

Table 5.12: Result of the sensitivity analyses of the decision tree model for Mpumalanga

Sensitivity analyses results	SP option	AS+SP option
Cost effectiveness ratio	**$24.05**	**$12.05**
Variable assumptions	Base Case	Base Case
Cost effectiveness ratio	**$27.65**	**$12.43**
Variable assumptions	*pHosp_SP* = 0.8	*pHosp_ASP* = 0.8
Cost effectiveness ratio	**$19.24**	**$11.54**
Variable assumptions	*pHosp_SP* = 0.1	*pHosp_ASP* = 0.1
Cost effectiveness ratio	**$16.27**	**$11.71**
Variable assumptions	*HospCostBaseline* calculated for 3 days of hospitalisation	*HospCostPostACT* calculated for 3 days of hospitalisation
Cost effectiveness ratio	**$24.05**	**$12.38**
Variable assumptions	*HospCostBaseline* calculated for 7 days of hospitalisation	*HospCostPostACT* calculated for 7 days of hospitalisation
Cost effectiveness ratio	**$21.78**	**$11.35**
Variable assumptions	Lowest antimalarial (SP) cost per malaria outpatient = $0.2	Lowest antimalarial (AS+SP) cost per malaria outpatient = $1.0
Cost effectiveness ratio	**$24.05**	**$13.6**
Variable assumptions	Highest antimalarial (SP) cost per malaria outpatient = $2.41	Highest antimalarial (AS+SP) cost per malaria outpatient = $3.24
Cost effectiveness ratio	**$22.23**	**$6.60**
Variable assumptions	Lowest baseline diagnostic cost per malaria outpatient = $0.5	Lowest post ACT diagnostic cost per malaria outpatient = $0.5
Cost effectiveness ratio	**$24.05**	**$13.34**
Variable assumptions	Highest baseline diagnostic cost per malaria outpatient = $2.27	Highest post ACT diagnostic cost per malaria outpatient = $7.21
Cost effectiveness ratio	**$18.42**	**$8.49**
Variable assumptions	Other cost per malaria outpatient excluded from the analysis (i.e. other costs = 0)	Other cost per malaria outpatient excluded from the analysis (i.e. other costs = 0)

Sensitivity analyses results	SP option	AS+SP option
Cost effectiveness ratio	**$24.05**	**$12.05**
Variable assumptions	Base Case	Base Case
Cost effectiveness ratio	**$257.01**	**$89.39**
Variable assumptions	Lowest effectiveness of SP monotherapy (i.e. cure rate = 12%)	Lowest effectiveness of AL (i.e. cure rate = 12%)
Cost effectiveness ratio	**$13.05**	**$12.04**
Variable assumptions	Highest effectiveness of SP monotherapy (i.e. cure rate = 99%)	Highest effectiveness of AL (i.e. cure rate = 99%)

Results in Table 5.12 show that the C/E ratios for the two treatment options (SP monotherapy and AS+SP) in Mpumalanga are sensitive to changes in some of the variables as was the case for the Kwazulu Natal decision tree results. For example, the C/E ratio for the SP monotherapy option is sensitive to changes in the values SP cure rate, other costs related to management of uncomplicated malaria (i.e. excluding costs of antimalarials and diagnostics), *pHosp_SP* (i.e. the probability that a patient who has failed to get cured with SP (first time) will seek care at a hospital and will be hospitalised to get second line treatment), *HospCostBaseline* (i.e. cost of treating one malaria inpatient which includes diagnostic, drugs and other costs at baseline). The lower the value of *pHosp_SP*, the lower the C/E ratio and vice versa. Similarly, results also show that the C/E ratio for SP will be significantly lower if malaria patients are only hospitalised for 3 days instead of 7 days. As expected the exclusion of 'other costs' results in a lower C/E ratio for SP, and vice versa, and the higher the cure rate of SP the lower its C/E ratio. Likewise, the C/E ratio for the AS+SP option is sensitive to changes in the values of the same variables (i.e. *pHosp_AL*, *HospCostPostACT*, and cure rate for AS+SP) in the same way. In addition, the cost-effectiveness ratio for the AS+SP option are highly sensitive to changes in the prices of AS+SP and to changes in the diagnostic costs. Of particular importance is the finding that the C/E ratio for the AS+SP option is highly sensitive to the exclusion of 'other costs' (i.e. $8.49 compared to $12.05 when the other costs are included), and to the changes in the diagnostic costs. However, it is important to note that C/E ratio for the AS+SP option remains lower than that for the SP option in all scenarios.

Figure 5.5: Sensitivity analysis on cure rate for SP and cure rate for ASP

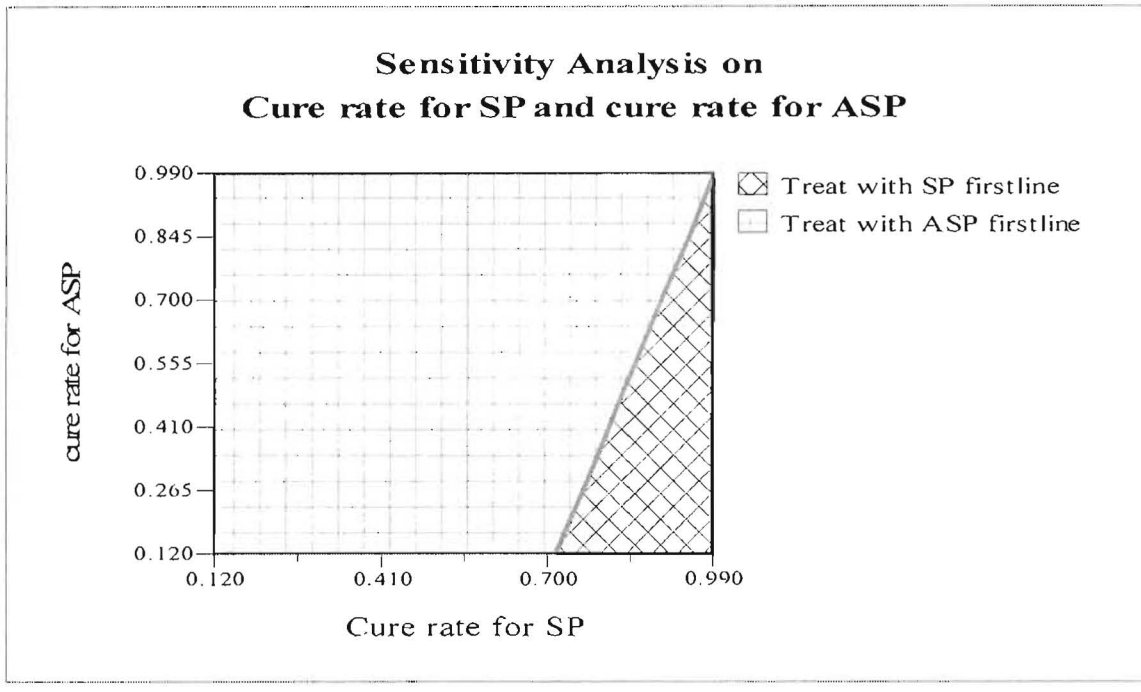
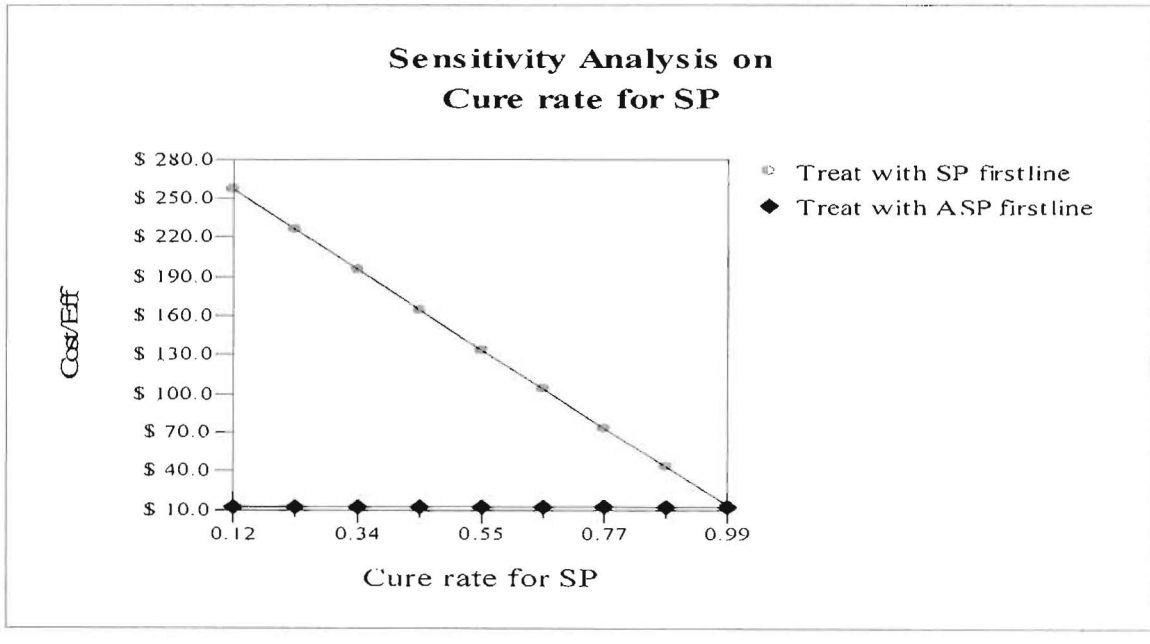


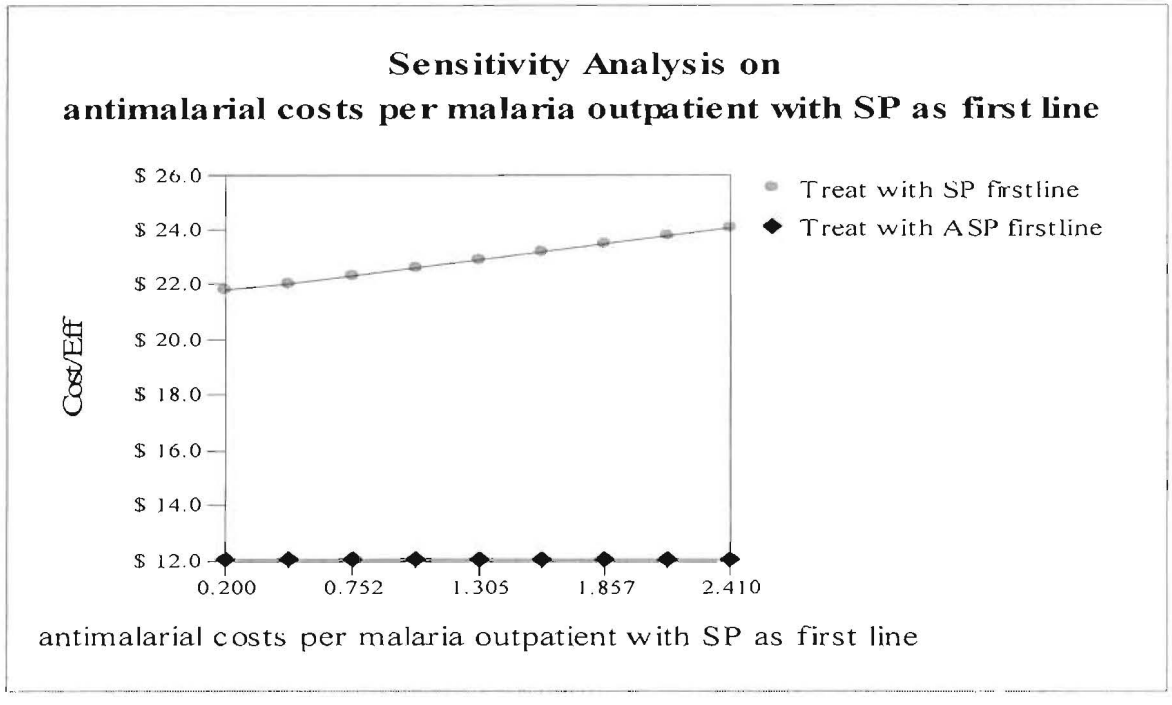
Figure 5.6 and 5.7 show the results of varying the values of SP cure rate and of the unit antimalarial costs per malaria outpatient. In Figure 5.6, sensitivity analyses results show that using AS+SP remains are more cost-effective alternative, compared to using SP monotherapy, even at very high levels of *SP cure rate* (e.g. 95%).

Figure 5.6: Sensitivity analysis on cure rate for SP



In Figure 5.7, sensitivity analysis results show that even when the antimalarial *cost per malaria outpatient* with SP is as low as US $ 0.2 (compared to the US $ 2.4 cost at baseline), using AS+SP as first line antimalarial remains highly more cost-effective than using SP monotherapy.

Figure 5.7: Sensitivity analysis on antimalarials costs per malaria outpatient with SP as first line



5.3.6: Comparisons with Kwazulu Natal Delphi estimates

In standard cost-effectiveness studies, the impact or expected impact of an intervention on health outcomes is assumed to be measured fairly easily because there is an implicit assumption that this will not be confounded by the impact of other interventions working either synergistically or against the intervention in question. As such, no standard methods have been advanced or recommended in the literature to deal with situations such as the one in Kwazulu Natal where the impact of a single intervention, had it occurred in isolation, could not be easily measured. Given this complexity, the Delphi technique was employed to provide estimates of the disaggregated impact of the 3 interventions in and around Kwazulu Natal.

Medians of the estimates provided by panellists were used to evaluate the cost-effectiveness of AL in Kwazulu Natal. In order to examine the validity of the estimates provided from the Delphi survey and conclusions reached on the cost-effectiveness analysis of AL, comparisons of the estimated impact of AL in Kwazulu Natal and AS+SP in Mpumalanga have been made. Such comparisons are considered to be acceptable because of the similarities in the study settings. For example, the epidemiology of malaria in Kwazulu Natal and Mpumalanga is similar; both study sites were using SP at baseline (albeit with different levels of efficacy); process of policy change, health systems & infrastructure and malaria control interventions are similar and both were changing to ACTs. The notable difference between the provinces was that vector control remained unchanged in Mpumalanga, but was considerably strengthened in Kwazulu Natal.

Table 5.13 provides a summary of the percentage reductions in malaria-related costs following the introduction of ACTs in Kwazulu Natal and Mpumalanga. There was a reduction in total malaria outpatient costs, of 88.9% and 66.3%, at clinic level in Kwazulu Natal and Mpumalanga, respectively, between baseline and post-intervention phases (Table 5.9). For Kwazulu Natal, AL was estimated to be responsible for 34.3% of the reduction in total malaria outpatient costs at clinic level. This percentage is comparable to the one for Mpumalanga clinics (66.3%).

At the hospital level, however, the percentage reduction in malaria-related costs (both outpatient and inpatient) attributable to AL in Kwazulu Natal is consistently lower than that attributable to AS+SP in Mpumalanga (see Table 5.13). Instead, the Mpumalanga reduction in malaria costs is more comparable to the reduction in costs in Kwazulu Natal attributed to all 3 interventions. Since the evaluations in Kwazulu Natal and Mpumalanga were undertaken 2 and 1 years, respectively, after the ACTs were introduced, we would expect reductions in costs in Kwazulu Natal to be greater than those in Mpumalanga. This suggests that the estimates obtained from the Delphi survey are likely to have under-estimated the contribution of AL to the reduction in malaria cases and admissions in Kwazulu Natal. In addition, the impact of introducing an IRS vector control programme in southern Mozambique, initially on the border of Kwazulu Natal and later on the Mpumalanga border, might have been underestimated for both South African study sites.

Table 5.13: Percentage reduction in malaria-related costs following ACTs in Kwazulu Natal and Mpumalanga

Reduction in clinic costs (baseline vs. ACT) of:	Outpatient malaria costs: Kwazulu Natal clinics	Outpatient malaria costs: Mpumalanga clinics	AL contribution in Kwazulu Natal
Antimalarials	86.8%	72.0%	48.6%
Diagnostics	68.6%	21.5%	47.0%
Other recurrent and capital costs	95.5%	74.4%	52.0%
TOTAL	88.9%	66.3%	34.3%

Reduction in hospital costs (baseline vs. ACT) of:	Outpatient malaria costs Kwazulu Natal	Outpatient malaria costs Mpumalanga	AL contribution in Kwazulu Natal
Antimalarials	80.8%	90.9%	46.3%
Diagnostics	58.6%	24.9%	5.2%
Other recurrent and capital costs	90.7%	84.0%	32.2%
TOTAL	89.1%	79.9%	27.0%

Reduction in hospital costs (baseline vs. ACT) of:	Inpatient malaria costs Kwazulu Natal	Inpatient malaria costs Mpumalanga	AL contribution in Kwazulu Natal
Antimalarials	87.4%	70.8%	20.2%
Diagnostics	56.7%	77.0%	45.4%
Other recurrent and capital costs	89.8%	93.7%	41.5%
TOTAL	89.3%	93.0%	41.0%

5.3.7: Limitations of study

As in the case of Kwazulu Natal, there were no reliable data on the quantities of antimalarials consumed at clinic and hospital levels. While it was easy to obtain information on quantities of ACTs purchased at hospital level and quantities sent to each clinic, it was difficult to determine the amounts actually consumed. Similarly, the limitations of the before-and-after study design, previously discussed in chapter 4 (see section 4.3.6) for Kwazulu Natal hold true for the analysis in Mpumalanga study sites. Furthermore, some comparisons between Kwazulu Natal and Mpumalanga have been difficult due to the contextual differences, especially on factors confounding the impact of ACTs. Lastly, the potential impact of IRS in southern Mozambique on malaria transmission and health outcomes, no matter how small, has not been studied or evaluated in Mpumalanga.

5.4: DISCUSSION AND CONCLUSIONS

Results in Tables 5.1 – 5.6 show that the change in treatment policy to AS+SP resulted in both improved health outcomes as well as reduced costs. This finding is similar to the findings reported in chapter 4, for the change from SP monotherapy to AL in Kwazulu Natal. From these two studies, it can be concluded that ACTs can be both cost-saving and cost-effective in settings that are similar to Kwazulu Natal and Mpumalanga. Although not many economic evaluations of ACTs have been conducted, similar conclusions around decreased transmission and resistance as an impact of ACTs have been reached by other studies conducted on the western border of Thailand which has similar characteristics as the study sites discussed here [24].

Results of the economic evaluation show that AS+SP is not only more cost-effective than SP monotherapy, but is also cost saving, even in the short-term. The introduction of AS+SP could potentially result in slightly greater cost-savings if the findings reported here are extrapolated to the entire province. However, the majority of malaria cases in Mpumalanga occur in the study districts. For instance, if we considered the total number of malaria cases for the entire province (Mpumalanga) in 2000 (i.e. 12,390) and in 2003 (i.e. 4,307) and using the baseline and post-ACT unit costs of $10.31 and $11.56 respectively, cost savings of $77,952 would be realised for the whole province, compared to the $69,174 calculated from the sampled health facilities.

The fact that ACTs (i.e. both artemether-lumefantrine and AS+SP) have been found to be both cost-saving and more cost-effective than SP monotherapy, even on the short term, is encouraging, particularly in light of the arguments around their relatively higher prices (compared to SP monotherapy). These findings do not incorporate the longer term potential benefits of ACT further reducing malaria transmission and possibly delaying antimalarial resistance. This implies that an economic case can be made as a justification for switching from a seemingly 'cheap' antimalarial to another one whose acquisition price is significantly higher. It has been shown from the analyses in this chapter that the ICER is actually interpreted as a '*reduction in malaria costs per malaria case averted*'. This means that, for both artemether-lumefantrine and AS+SP, when compared to SP monotherapy, savings are made (at both outpatient and inpatient levels) because the use of these

very effective antimalarials (even in the short-term) results in a massive reduction in malaria cases, admissions and deaths. Not surprisingly, AS+SP has the potential of being more cost-effective than artemether-lumefantrine. This is possible because AS+SP is relatively cheaper than artemether-lumefantrine and yet they have been shown to have the same efficacy (99%) in curing uncomplicated malaria patients, in Kwazulu Natal and Mpumalanga. It is important to note, however, that if AS+SP is used in places where resistance to SP monotherapy is higher than that in Mpumalanga, its effectiveness in reducing the number of malaria cases and admissions will be reduced. In such a case, artemether-lumefantrine, despite being more expensive than AS+SP, might be more cost-effective, especially in the long run. Arguing from another angle, there it is possible that the ICER (i.e. the cost-saving per admission averted) for AS+SP (at inpatient level) is significantly higher than that for artemether-lumefantrine (at inpatient level) because of the different admission policies and practices in Mpumalanga and Kwazulu Natal. As noted earlier, Mpumalanga was admitting more people and therefore it is possible that there is more cost-savings associated with AS+SP because of the changes in the admission practices as opposed to the effectiveness of AS+SP per se.

The inclusion of '*other recurrent and capital costs*' in the calculation of costs of managing malaria patients is of critical relevance. On one hand, in comparative studies, such as this one, the inclusion of other recurrent and capital costs highlights the differences in cost structures, staffing levels, and case management practices (such as admission policies, diagnostic approaches, etc) among others. On the other hand, however, the inclusion of other recurrent and capital costs can lead to unexpected results that are not related to the cost of antimalarials but to fundamental differences in health service provision in different contexts. Further, the inclusion of other recurrent and capital costs is important in contexts with lower than average health service utilisation (indicating substantial unmet need, particularly in Kwazulu Natal with a heavy AIDS burden) and that the cost savings represent the opportunity cost of not meeting non-malaria health needs adequately.

Despite having a direct impact on reducing malaria cases, findings from both Kwazulu Natal and Mpumalanga have shown that ACTs could potentially have a positive impact on severe malaria given the low levels of treatment failure and hence cases progressing to severe disease. This indirect impact on severe disease results in even further and greater cost savings at malaria inpatient level

(Table 5.8). Several malaria control activities play a role in maintaining low malaria prevalence rates in Mpumalanga and Kwazulu Natal. The lack of major confounding factors in Mpumalanga has enabled the application of standard economic evaluation techniques in establishing whether AS+SP is cost-effective or not. However, it is possible that the introduction of IRS in southern Mozambique (described in chapter 4) might have had some indirect impact on malaria health outcomes in Mpumalanga.

Results presented in this chapter have also shown that with comparative studies, it is important to establish the underlying causes of the differences in costs that arise from systemic and operational activities, as opposed to those arising from the interventions being studied. For example, it has been demonstrated that while unit costs (i.e. average cost effectiveness ratios) for malaria outpatient cases are largely similar in Mpumalanga (for AS+SP) and Kwazulu Natal (for artemether-lumefantrine), the unit costs for malaria inpatients (where drug treatment policy did not change in either Kwazulu Natal or Mpumalanga) are significantly different. The reason for this lies in the admission policies in the hospitals in the different provinces, with Mpumalanga having a more conservative admission policy that largely admits a good number of uncomplicated cases of malaria (who would often be treated as outpatients in Kwazulu Natal) for inpatient care in an attempt to limit the number of malaria deaths.

In both the Kwazulu Natal and Mpumalanga studies, the costs of changing policy are minimal because the well-established and functional Department of Health and their Malaria Control Programs undertook most activities as part of routine work. In settings where health systems are inadequate and where the scale of the malaria burden is much higher, change of policy would require significant additional resources, and the cost-savings that might potentially result from the introduction of ACTs could be eroded by high implementation costs. A key difference between South Africa and many African sites is that treatment care-seeking for malaria largely takes place in the private sector (as opposed to the public sector). The phenomenon of seeking care in the informal and private sectors poses serious challenges in terms of costs and feasibility of effective policy change in other African settings.

Furthermore, within both provinces, access to health facilities was pretty similar, with most households living within 5 km from a health care facility. Although the benchmark of "5km to a health facility" is generally taken as adequate by international standards, several aspects of "access" need to be considered when evaluating adequacy and accessibility to health care. For instance, the fact that in both provinces "walking" is the commonest method of travel to health facilities raises a few concerns when one considers that a sick patient would have to walk 5km to reach care. Other key aspects that need to be considered in "treatment seeking" are "waiting time" at facilities, staff attitudes and availability of appropriate and adequate care for a specific illness. The evaluation of staff attitudes and availability of adequate care were not part of the household surveys. However, one of the key findings of these surveys is the high level of seeking malaria treatment at public clinics. In both provinces, 99% of all the people who reported having ever had malaria had sought care for the illness, 95% of which had sought care at public health facilities. Only 1% and 2.5% of the people sought malaria treatment from private practitioners in Kwazulu Natal and Mpumalanga respectively. The low prevalence of treatment seeking outside of the public sector facilitated a high coverage of ACT treatment, a key component of ACTs achieving optimal reductions in malaria transmission (and potentially delaying resistance) in both sites.

Comparing the findings of the economic evaluation studies in Kwazulu Natal and Mpumalanga, shows that the Delphi technique, while helpful in quantifying phenomenon that are otherwise difficult to measure, probably under-estimated the impact of the artemether-lumefantrine intervention alone in Kwazulu. This is possibly due to either the composition of the Delphi team or to the information (particularly on the timing of the implementation of the 3 interventions in Kwazulu Natal – see Figure 4.2) that was provided to panellists during the survey period. In fact, findings show that the percentage changes in health outcomes in Mpumalanga (associated with the change from SP monotherapy to AS+SP) are more comparable to the percentage changes of the 3 interventions in Kwazulu Natal, and are much higher than changes attributed by the Delphi survey to the artemether-lumefantrine intervention alone in Kwazulu Natal.

6. DETERMINANTS OF THE COSTS AND COST EFFECTIVENESS OF ROUTINE RAPID DIAGNOSTIC TESTING IN MANAGING UNCOMPLICATED FALCIPARUM MALARIA WITH ARTEMISININ-BASED COMBINATION THERAPY

6.1: INTRODUCTION

A prompt and accurate diagnosis is the key to early effective malaria case management. Historically, the two diagnostic approaches commonly used were clinical diagnosis and microscopic diagnosis [155]. In most endemic countries, diagnosis of malaria and thus administration of antimalarial treatment has been predominantly based on clinical diagnosis [2, 7, 57-60]. More recently the use of rapid diagnostic tests (RDT) has been explored in several places [57, 58, 82, 88-91, 154, 181-186]. Clinical diagnosis has a key advantage (over other diagnostic techniques) of being cheap and easy to perform in rural settings and by those with minimal skills. Clinical diagnosis is cheap because it does not require any equipment. In addition, the diagnostic results are achieved relatively quickly (compared to other forms of diagnosis where a health worker has to wait for test results), hence allowing for quick provision of antimalarial treatment. Clinical diagnosis is, however, likely to result in erroneous treatment of millions of non-malaria cases [61]. Misdiagnosis of malaria is costly as it can result in considerable morbidity and mortality, by contributing to both a delay in treatment of the correct diagnosis and through increasing antimalarial drug pressure and thus resistance, speeding up the obsolescence of affordable drugs [58, 59, 61].

Definitive diagnosis, when used correctly, can contribute to better and more cost-effective disease management and can reduce the unnecessary and irrational use of antimalarial drugs. Although microscopy is considered to be the gold standard for malaria diagnosis [2, 7, 57-59, 62, 82, 85] and has several advantages over the other diagnostic approaches, it has been found to be operationally impractical in rural or resource-poor settings due to its personnel and technical requirements of infrastructure, equipment, regular supply of reagents and continued quality assurance supervision [2, 57, 58, 82]. Rapid diagnostic tests, particularly where accurate microscopy is not accessible, offer the possibility for accurate and accessible detection of malaria parasites and have an important role in

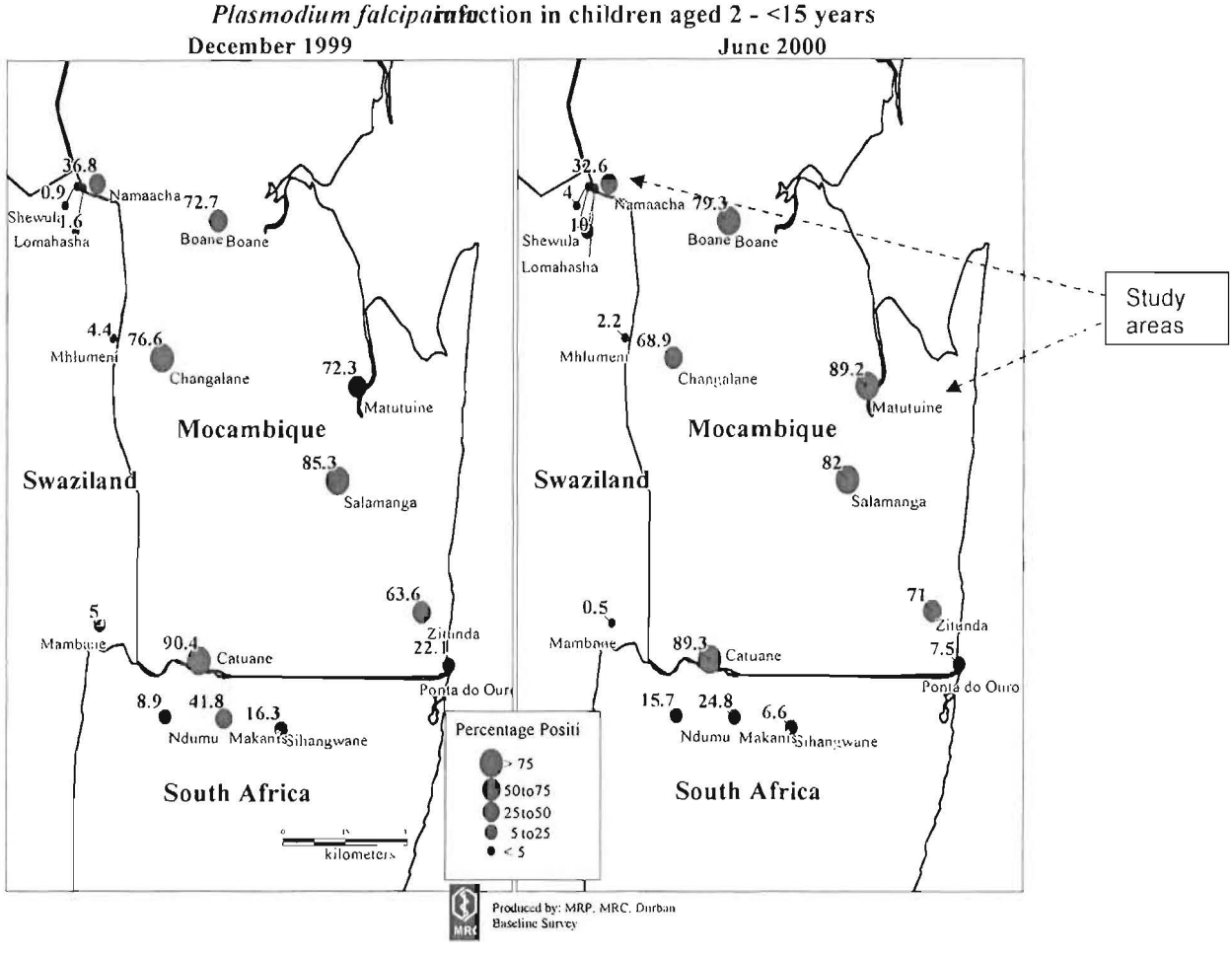
limiting malaria over-diagnosis, and in promoting more rational use of increasingly costly antimalarials. Extensive resistance to chloroquine, sulphadoxine-pyrimethamine and amodiaquine monotherapy has prompted malaria treatment policy change to more expensive combinations, especially artemisinin-based combination therapy (ACT) [187]. Widespread use of artemisinin-based combination therapy has been shown to decrease malaria transmission in South Africa [73] and Thailand [24]. Similarly, high coverage with effective indoor residual spraying programmes [188] or insecticide treated bed nets [189, 190] have resulted in sustained reductions in malaria risk. It is unclear to what extent the use of definitive diagnosis (mainly using RDTs) as the basis for ACT treatment contributed to the cost effectiveness and cost savings described in Chapters 4 and 5, as definitive diagnosis had been routine since 1996 – well before the introduction of the ACT policy.

The role of definitive diagnosis or rapid diagnostic tests is more uncertain in areas with high intensity malaria transmission. In areas of high intensity malaria transmission, it has been considered acceptable to treat on a clinical basis on the rational grounds that a high proportion of febrile cases are actually malaria cases and that it is better to treat all febrile cases than to miss one potentially fatal infection especially in children younger than 5 years old [191]. This argument was logical from an economical perspective when cheap traditional antimalarials were used for treating uncomplicated malaria. Following the emergence and spread of resistant to most of these cheap antimalarials and the subsequent use of relatively more expensive antimalarials (e.g. ACTs), it is unlikely to be cost-effective to use antimalarials irrationally by treating all febrile cases (without testing for malaria) with expensive antimalarials. Within the context of increasing antimalarial costs and or decreasing malaria transmission, the importance of limiting antimalarial treatment to only those confirmed as having malaria parasites becomes paramount [2, 7, 58]. This motivates the assessment of the cost-effectiveness of routine use of definitive diagnosis as an integral part of the assessment of the cost-effectiveness of deploying artemisinin-based combination therapies, particularly in contexts of effective vector control and low to moderate intensity malaria transmission.

The assessment of the cost-effectiveness of ACTs, presented and discussed in chapters 4 and 5 was based on information from 2 South African study sites. In South Africa where the intensity of malaria transmission has become very low following five decades of intensive malaria control, definitive

diagnosis (RDTs or microscopy) was established as standard practice in all public health facilities in 1996, well before the change of first line treatment policy to ACTs. For this reason, it was not possible to assess the cost-effectiveness of RDTs in South African study sites. Given this, routine use of definitive diagnosis (using RDTs) as of the basis for treating uncomplicated malaria in areas of higher intensity malaria transmission was investigated in southern Mozambique. The potential costs and cost effectiveness of routine rapid diagnostic tests were explored for two pilot districts (Namaacha and Matutuine) following the introduction of effective vector control (October 2000) but prior to the deployment of ACTs and RDTs, to inform policies and planning relating to diagnosis and management of uncomplicated malaria in Maputo Province, southern Mozambique.

Figure 6.1: Map of Southern Mozambique showing malaria prevalence in study sites (1999-2000)



This chapter compares the costs and cost-effectiveness of clinical and definitive malaria diagnosis using *rapid diagnostic tests* as the basis for treatment with ACTs within all public sector health centres (similar to the south African district hospitals) and health posts (similar to the South African clinics). Data used for the analyses in this chapter were obtained from two districts in southern Mozambique, Namaacha and Matutuine. Both districts were in holoendemic malaria transmission areas with *P. falciparum* prevalence (among children aged 2-15 years) of over 60% prior to the implementation of a high coverage community-based indoor residual spraying (IRS) programme in 2000 (Figure 6.1). This evaluation has been focused on the use of RDTs in all clinically diagnosed malaria cases and in those patients over 6 years of age only. The effect of limiting the use of RDTs to patients older than 6 years was considered because their antimalarial treatment cost is relatively more expensive than that of children 6 years or younger. Furthermore, as a result of acquired immunity increasing with age in areas of moderate to high intensity malaria transmission, malaria is a less prevalent cause of severe illness in the older age groups. The use of two differently priced artemisinin-based combination therapies, artesunate-SP (AS+SP) and artemether-lumefantrine (AL) has been evaluated and compared. Since the prices of artesunate-amodiaquine (AS+AQ) are identical to those of AS+SP, the conclusions reached for AS+SP can be extended to AS+AQ.

The remaining part of the chapter is structured as follows: Section 6.2 describes the methods used in collecting and analysing cost and effectiveness data; the findings of the study are presented in section 6.3. The study limitations are presented in section 6.4, and the findings discussed in section 6.5.

6.2: METHODS

In 2001, before the implementation of ACTs (AS+SP) and RDTs at all public health facilities in the 2 pilot districts (Namaacha and Matutuine) in southern Mozambique, relevant baseline data on costs and health outcomes were collected from all the health facilities in the 2 districts, which comprised of 13 health posts and two health centres. Costing was undertaken from a public sector provider's perspective and includes all recurrent costs associated with treating malaria outpatients. Capital costs have been excluded from this analysis since RDTs do not require special equipment and/or additional infrastructure.

Without definitive diagnosis the actual number of true malaria cases is unknown, however the number of suspected malaria cases (based on clinical diagnosis) is known. In this study, data for the year 2002 on number and age distribution of febrile patients (suspected malaria cases) were obtained from the provincial and district Ministry of Health records in the 15 health facilities studied. To evaluate the impact of introducing definitive diagnosis using RDTs, 5 scenarios were considered based on the assumption that the use of *definitive* diagnosis would find that either 25%, 33.3%, 50%, 66.6% or 75% of the clinically diagnosed malaria (febrile cases) patients are confirmed to be actual malaria cases (i.e. after testing *positive* for malaria). The rationale for considering the 5 scenarios is to ascertain the cut-off point below which the introduction of RDTs is cost-effective or cost-saving, i.e., when clinical diagnosis is relatively 'more expensive' than definitive diagnosis. The use of these proportions across all age groups assumes that testing positive is constant across all age groups, which is a limitation of this analysis. In areas of intense malaria transmission the proportion of RDT positive patients may be expected to decrease with age as partial immunity is required.

ACT treatment dosages (and thus costs) are dependent on patient age or weight. Data on the age-breakdown of the fever patients presenting at Mozambican health facilities in 2003 (in the 2 study sites) were obtained for the AS+SP dosage categories and were adapted to fit the treatment schedule for artemether-lumefantrine (the recommended second line treatment in southern Mozambique during the pilot implementation of ACTs). The age distributions are presented in Table 6.1. Children under 1 year of age were excluded from this analysis as the Maputo provincial guidelines recommend that this high risk group is admitted to the health centre for treatment with quinine.

Table 6.1: Age distribution of patients with clinically diagnosed malaria in Namaacha and Matutuine districts, southern Mozambique

AS+SP		artemether-lumefantrine		
Age	Observed percentage (n= 31,438)	Age	Estimated Percentage	Basis
1-6 years	8,882 (28.3%)	1-5 years	23.6%	As for AS+SP, less 4.7% to cater for 6 year olds
7-13 years	4,814 (15.3%)	6-8 years	9.1%	As for AS+SP, plus 4.7% to include 6yrs, minus 10.9% to exclude 9-13years
14+ years	17,742 (56.4%)	9-12 years	8.7%	100- the others
		13+ years	58.6%	As for AS+SP, plus 2.2% to include 13 year olds
	100%		100%	

6.2.1: Calculating Costs

The number of malaria cases for each scenario is calculated on the basis of the number of suspected malaria cases obtained from records in all 15 public sector health facilities in the two study sites. The calculation of costs is based on number of suspected malaria cases and the calculated malaria cases for each scenario of definitive diagnosis considered. All febrile cases that are negative for malaria would probably then be treated for some other illness. However, the estimation of treatment costs for non-malaria febrile cases was beyond the scope of this study and is therefore not discussed. The exclusion of these costs could mean that the cost-savings (and hence the cost-effectiveness of RDTs) are over-estimated.

6.2.1.1: Cost of Antimalarials

Data on prices of antimalarials were obtained in 2003/04. In the analyses, the costs of AS+SP and artemether-lumefantrine have been calculated as *unit price* multiplied by the estimated *quantity of antimalarials* consumed. Quantities of antimalarials "consumed" have been calculated from the number of malaria cases (in a given age group) *multiplied by* the number of tablets recommended for a full treatment course (for that age group).

Since SP is administered as a single dose and artesunate is taken daily for three days, AS and SP are priced and distributed separately. The unit price of artesunate is based on the cost of the only artesunate product currently pre-accredited by the WHO, namely Arsumax®, produced by Sanofi-Aventis, Paris, France of USD 30 (for 25 blister packs of 12 tablets each). The price at which Mozambique had ordered SP (Fansidar®, a fixed dose combination of 500mg sulphadoxine plus 25mg pyrimethamine manufactured by Roche, Johannesburg South Africa) for the pilot ACT deployment of $0.19 per tablet, was used in the analyses. The unit prices for a treatment course of AS+SP, for each age group, are presented in Table 6.2.

The unit prices of artemether-lumefantrine are based on the WHO preferential price [192] and are presented in Table 6.3. Unlike AS+SP, AL is co-formulated as a fixed dose combination of 20mg artemether and 120mg lumefantrine.

Table 6.2: Prices for AS+SP

Group	Price per treatment course (AS+SP)*	Number of tablets for full course treatment
1-6 years	$0.49	3 AS + 1 SP
7-13 years	$0.98	6 AS + 2 SP
14+ years	$1.77	12 AS + 3 SP

* With the price per tablet of SP at $0.19 and price per tablet of AS at $0.1 (prices at which MOH procured AS-SP)

Table 6.3: Unit Prices for AL

Group	Price per treatment course (AL)*	Number of tablets for full course treatment
10-14 kg (1-5 yrs)	$0.90	6
15-24 kg (6-8 yrs)	$1.40	12
25-34 kg: (9-12 yrs)	$1.90	18
35+kg: 13+ years	$2.40	24

*WHO preferential prices

6.2.1.2: Calculating costs of RDTs

For previous surveys in the study area, the Mozambique Ministry of Health was using RDTs (ICT Diagnostics PF Tests ML01®), where a box of 25 RDT tests was obtained at a price of $23.72. This translates into a unit price of USD 0.95 (2003 prices). In the analyses, the cost of RDTs was calculated as the *unit price* multiplied by the estimated *quantity of RDTs used*. 'Quantity of RDTs used' was estimated to be equal to the number of clinically diagnosed malaria cases in 2001 (as described below in Section 6.2.2). This estimation was made on the assumption that each clinically diagnosed case would be tested using one RDT.

6.2.1.3: Calculating "other costs of treatment"

Apart from antimalarials and diagnosis, treatment of malaria patients consumes other resources, such as health worker time, space and other resources at the health facility. Information on total health facility expenditure was obtained for the year 2001 and these "other recurrent costs" were then inflated to 2003 prices to ensure consistency with the cost of antimalarials and RDTs. "Other recurrent costs" include personnel, utilities, administration, maintenance, and transport (i.e. excluding antimalarial drugs and diagnostic tests as these costs were calculated separately). Using the step-down method, cost data were first allocated between the **outpatient** and **inpatient** departments, and then *outpatient costs* were allocated to malaria on the basis of *proportion of malaria outpatient to total facility outpatient visits*. The allocation factor for each scenario was different, calculated as either the number of clinically diagnosed or the confirmed malaria cases (for each scenario) as a proportion of total facility outpatient visits. "Other recurrent costs allocated to malaria" were calculated as the *health facility outpatient expenditure* multiplied by the *allocation factor*.

6.2.1.4: Costing under the different Scenarios

Given the reliance on clinical diagnosis of malaria, *actual* malaria incidence in most sub-Saharan countries is not known. Analyses presented in this chapter focus on a wide range of scenarios reflecting varying levels of malaria endemicity. The analyses presented in this chapter have considered the following scenarios[19]: that 25%, 33.3%, 50%, 66.6% and 75% of the clinically

[19] Using these scenarios assumes that the proportion of those testing positive is the same across all age groups.

diagnosed (febrile) cases would be malaria positive when a definitive diagnostic test is used. Steps followed in calculating costs under the different scenarios were as follows:

(a) FOR USE OF RDTs

1. Calculate the 'actual' number of malaria cases; that is, the number of clinically diagnosed malaria (febrile) cases that would be malaria positive after the test based on the different scenarios (i.e. 1/4, 1/3, ½, 2/3, ¾). For example, if a total of 25,000 patients presented with fever or were suspected to have malaria, then for the scenario where ¼ (or 25%) would be found positive, "number of malaria cases" would be ¼ x 25,000 (= 6250 actual malaria cases).

2. Breakdown the number of malaria cases into the different age groups (see Table 6.1). For example, for the 25% scenario, the 'number of malaria cases that would be confirmed positive' (i.e. 6250) are then distributed between the different age categories: 1-5, 6-8, 9-12 and 13+ years, based on the age proportions in the study population presented in Table 6.1.

3. Calculate the quantity of antimalarials that would be consumed by each age group; that is, number of malaria cases in each age category *multiplied by* the number of tablets recommended for that age group;

4. Calculate costs of antimalarials (price x quantity of antimalarials for each age group, then sum for all age groups);

5. Calculate costs of RDTs = $0.95 (Unit price for ICT ML01®) *multiplied by* all clinically diagnosed malaria (fever) cases (from the above example, this would be 25,000 cases)

6. Total costs1 = Cost of antimalarials + Cost of RDTs, i.e. 4 + 5 above

7. Calculate "other treatment costs" taking into consideration the proportion (%) of malaria cases to total health-facility outpatients (% for each scenario is different).

8. Total costs2 = Cost of Antimalarials + Cost of RDTs + 'Other recurrent costs'

This is likely not to be the case always.

(b) FOR CLINICAL DIAGNOSIS

1. Number of 'malaria cases' = total number of fever cases seen at the facility
2. Breakdown the fever cases into the different age groups according to the age distribution recorded for suspected malaria cases in the health facility records (see Table 6.1)
3. Calculate the quantity of antimalarials that would be consumed by each age group; that is, number of malaria cases in each age category *multiplied by* the number of tablets recommended for that age group;
4. Calculate costs of antimalarials (price x quantity of antimalarials for each age group, then sum for all age groups);
5. Cost of RDTs = 0. There are no cost for RDTs since patients are diagnosed clinically
6. Total cost3 = Cost of antimalarials + 0 (Note that RDT cost in this scenario = 0)
7. Calculate "other treatment costs" taking into consideration the proportion of clinically diagnosed malaria (fever) cases to total facility outpatients.
8. Total costs4 = Cost of antimalarials + 0 + "other treatment costs".

The above calculations were done from two perspectives: for the use of RDTs in (a) all clinically diagnosed malaria (fever) patients and (b) only patients over 6 years of age.

6.2.2: Calculating Health Outcomes

Health outcomes in this chapter are the *actual number of malaria positive cases treated*. Data on total annual outpatient visits and number of **suspected malaria cases** for the year 2001 were obtained from facility records in the two districts studied in southern Mozambique, comprising two health centres (peripheral district hospitals) and 13 health posts (peripheral clinics). The number of suspected malaria cases recorded form the basis for calculating the health outcomes in each scenario (*of definitive diagnosis*), as well as the basis for calculating costs of the *clinical diagnosis* scenario. For each of the definitive diagnosis scenarios described above (i.e. 25%, 33.3%, 50%, 66.6% and 75%), the "actual" malaria cases were calculated. For example, for the *25% scenario* (that is, if 25% of fever patients tested positive for malaria), the *"actual" number of malaria cases* would be ***25%*** of the *number of suspected malaria cases*. Health outcomes were calculated for all scenarios in

the same way. After calculating the 'actual' number of malaria cases for the 25% scenario, this number would then be broken down into the different age groups. The 'actual' number of malaria patients in each age group was calculated on the basis of the percentages presented in Table 6.1, that were derived from the age distributions of clinically suspected malaria cases presenting at all 15 public sector health facilities in the study area.

6.2.3: Calculating Cost-effectiveness / Cost-savings

Total cost savings (or incremental costs) were calculated as the difference between the total costs under the different RDT scenarios and the total costs if clinical diagnosis is used. For example, the total cost of performing RDTs on all patients presenting with fever and only treating those confirmed as malaria cases with AS+SP is compared with the total cost of treating all clinically diagnosed malaria (fever) cases with AS+SP. The same comparison is undertaken for artemether-lumefantrine.

Incremental costs per malaria positive case treated (ICER) has been calculated as *incremental costs* divided by *number of malaria positive cases treated* for a given scenario.

6.2.4: Sensitivity Analyses

Sensitivity analyses were performed to assess whether the results are sensitive to changes in the price of RDTs, price of ACTs and the age distribution of febrile patients. Variations in the probability of clinically suspected malaria being confirmed are already explored by the range in "scenarios" from 25 to 75%. The initial set of assumptions, as described in the methodology above, is referred to as the 'base case' in the results section. One-way sensitivity analyses were performed to assess the impact of changes in one parameter (e.g. price of RDT, price of ACTs, and age distribution) on the cost-effectiveness of RDTs. Multi-way sensitivity analyses were performed to assess whether simultaneous changes in more than one variable would significantly change the cost-effectiveness results.

Since it is expected that prices of ACTs will reduce, rather than increase in the future, prices of ACTs lower than the ones in the base case scenario have been considered for sensitivity analyses. The lowest published ACT price to date was of an adult treatment course of dihydroartemisinin-piperaquine costing under US$1.00 per adult treatment. The international median price per tablet of SP USD 0.0257 [193] and of artesunate costing $0.077 per tablet were considered. For AL prices these were arbitrarily assumed to be 40% less than base case prices (i.e.: full dose per age group of $0.54, $0.84, $1.14 and $1.44).

For the sensitivity analysis of Rapid diagnostic tests, the lowest current cost of quality-assured rapid diagnostic tests, which is US$ 0.65 (e.g. Paracheck®, Orchid Biomedical, India), was used.

Three alternative age distributions were explored in the sensitivity analysis (Table 6.4), increasing the proportion of children in Age Breakdown 1 and 2, and increasing the adult population in Age Breakdown 3. These reflect populations with higher birth rates and those dominated by migrant worker adults.

Table 6.4: Age breakdown for base case and for three sensitivity analyses.

Base case Age breakdown	for ASSP 28.3%; 15.3%; 56.4% and for AL 23.6%; 9.1%; 8.7%; 58.6%
Age breakdown 1	for ASSP 50%; 15%; 35% and for AL 45%; 9%; 9%; 37%)
Age breakdown 2	for ASSP 40%; 20%; 40% and for AL 35%; 11.5%; 11.5%; 42%
Age breakdown 3	for ASSP 10%; 5%; 85% and for AL 5%; 4.5%; 4.5%; 86%

Table 6.5 provides a summary of the values used in the multi-way sensitivity analyses for each variable. In *multi-way 1* sensitivity analysis, lower prices of ACTs, RDTs and *age breakdown 1* (highest proportion of fever cases being children 6 years or younger) were considered. In *multi-way 2* sensitivity analysis, high prices of ACTs and RDTs and *age breakdown 3* (lowest proportion of fever cases being children younger than 6 years) were considered. In *multi-way 3*, high prices of ACTs (base case prices), low prices of RDTs and *age breakdown 1* were considered. In *multi-way 4* sensitivity analysis, low prices of ACTs and RDTs and the *base case age breakdown* were considered.

Table 6.5: Values of the variables considered for the sensitivity analyses

	Price of SP (per tablet)	Price of AS (per tablet)	Price of AL (per adult dose)	Price of RDTs	Age breakdown
Base case	$0.19	$0.10	$2.40	$0.95	base case
Multiway 1	$0.0257	$0.10	$ 1.44 (40% less than base-case price)	$0.65	1
Multiway 2	$0.19	$0.10	$2.40	$0.95	3
Multiway 3	$0.19	$0.10	$2.40	$0.65	3
Multiway 4	$0.0257	0.077	$ 1.44 (40% less than base-case price)	$0.65	base case

6.3: RESULTS

This section presents the results of the analyses of the costs and cost-effectiveness of using RDTs to limit the use of ACTs to those who actually have malaria, under different scenarios including different settings of malaria parasite prevalence (25% - 75%) among clinically suspected malaria cases. Analyses presented include:

a) the evaluation and comparison of two differently priced ACTs;

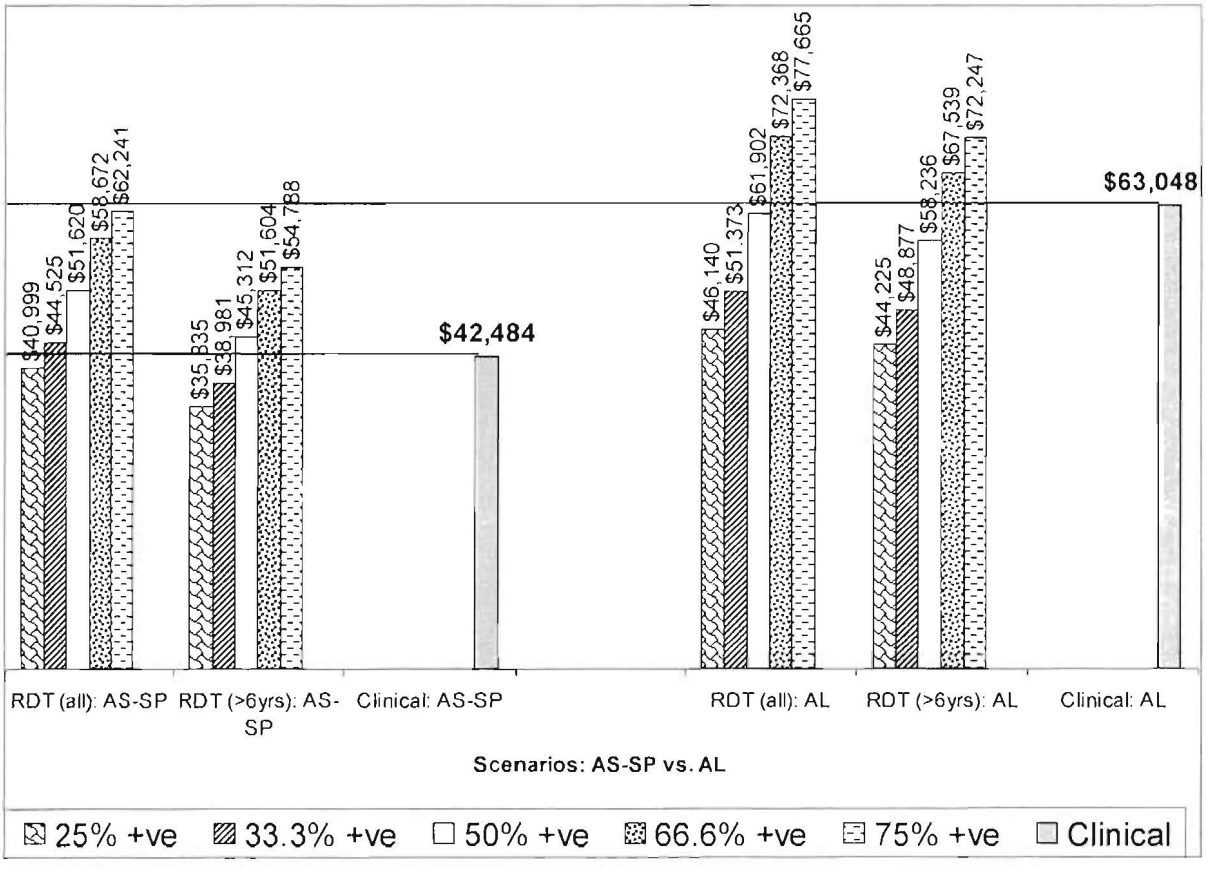
b) the evaluation of RDTs with a focus on (i) when they are restricted to a specific age group (> 6 years) and (ii) when they are used in all fever patients, and

c) the evaluation where "other recurrent costs" associated with treating uncomplicated malaria are (i) included and (ii) excluded from the analysis.

Figure 6.2 shows the total costs of antimalarials and diagnosis under the different scenarios. For the relatively cheaper ACT (AS+SP), only when 29% or less of all suspected malaria cases test positive for malaria will the use of *RDTs in all fever cases* result in lower treatment costs (i.e. cost savings), compared to when patients are treated on the basis of clinical diagnosis. The percentage increases from 29% to about 41.5% when use of RDTs is restricted to only those older than 6 years of age, in the case of AS+SP. On the other hand, for the relatively more expensive ACT (e.g. artemether-

lumefantrine), as long as fewer than 52% of tested cases are found to be positive, the use of RDTs in all suspected malaria cases will result in lower treatment costs (cost savings) compared to when patients are treated on the basis of clinical diagnosis. This percentage increases from 52% to 59% when the use of RDTs is restricted to those over 6 years of age (Figure 6.2).

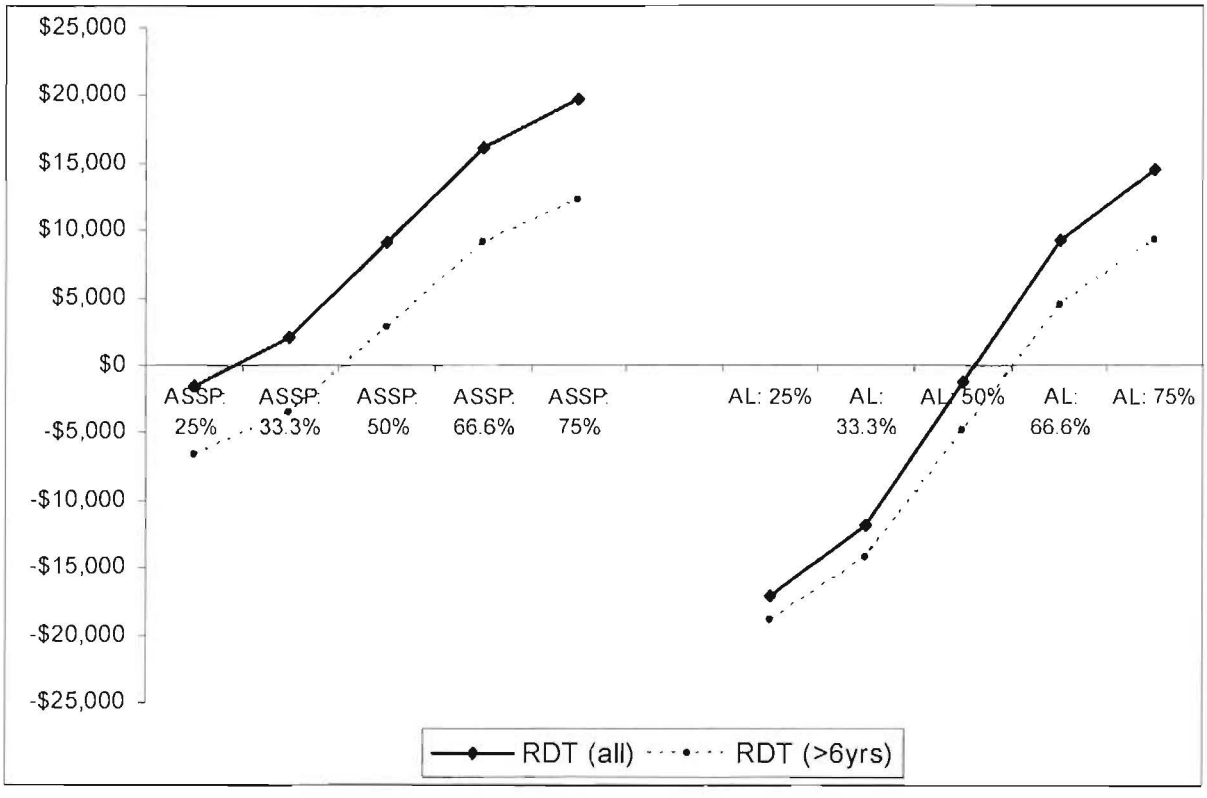
Figure 6.2: Total cost of antimalarials and RDTs: comparing Clinical and Definitive diagnosis



Similarly, Figure 6.3 confirms that introducing definitive diagnosis as part of malaria case management results in relatively higher *cost savings* or lower *additional costs* when a more expensive ACT (e.g. artemether-lumefantrine) is used to treat malaria patients compared to the relatively cheaper ACT (AS+SP). These results show that the more expensive the antimalarial being used for treating malaria patients, the more economic sense it makes to restrict antimalarials to those who truly need them. Limiting the use of RDTs to patients who are over 6 years of age results in lower *additional* costs and/or higher *cost savings* compared to when RDTs are used in all suspected

malaria cases, for both AS+SP and artemether-lumefantrine. However, in terms of cost, there are greater gains in restricting use of RDTs in patients over 6 years of age, when treating with a relatively cheaper ACT (e.g. AS+SP). This is depicted by a larger shift of the 'RDT all' (solid) curve to the right for AS+SP alternative compared to the relatively smaller shift for the AL alternative (Figure 6.3). This is because the price of one RDT ($0.95) is nearly twice as high as the cost of one dose of AS+SP for a patient younger than 6 years ($0.49) but similar to the cost of an AL treatment course for this age group ($0.90). Hence, treating all patients younger than 6 years (with AS+SP) on a clinical basis makes more economic sense than using an expensive RDT to test this age group. Figure 6.3 only considered the costs of the ACTs and RDTs without considering "other recurrent costs" associated with treating malaria patients.

Figure 6.3: Incremental costs (or cost savings) associated with use of RDTs when malaria is confirmed in varying proportions of patients for two ACTs (AS+SP and artemether-lumefantrine); excluding 'other recurrent costs'.



Note: The positive figures are incremental (additional) costs, while the negative figures are cost savings.

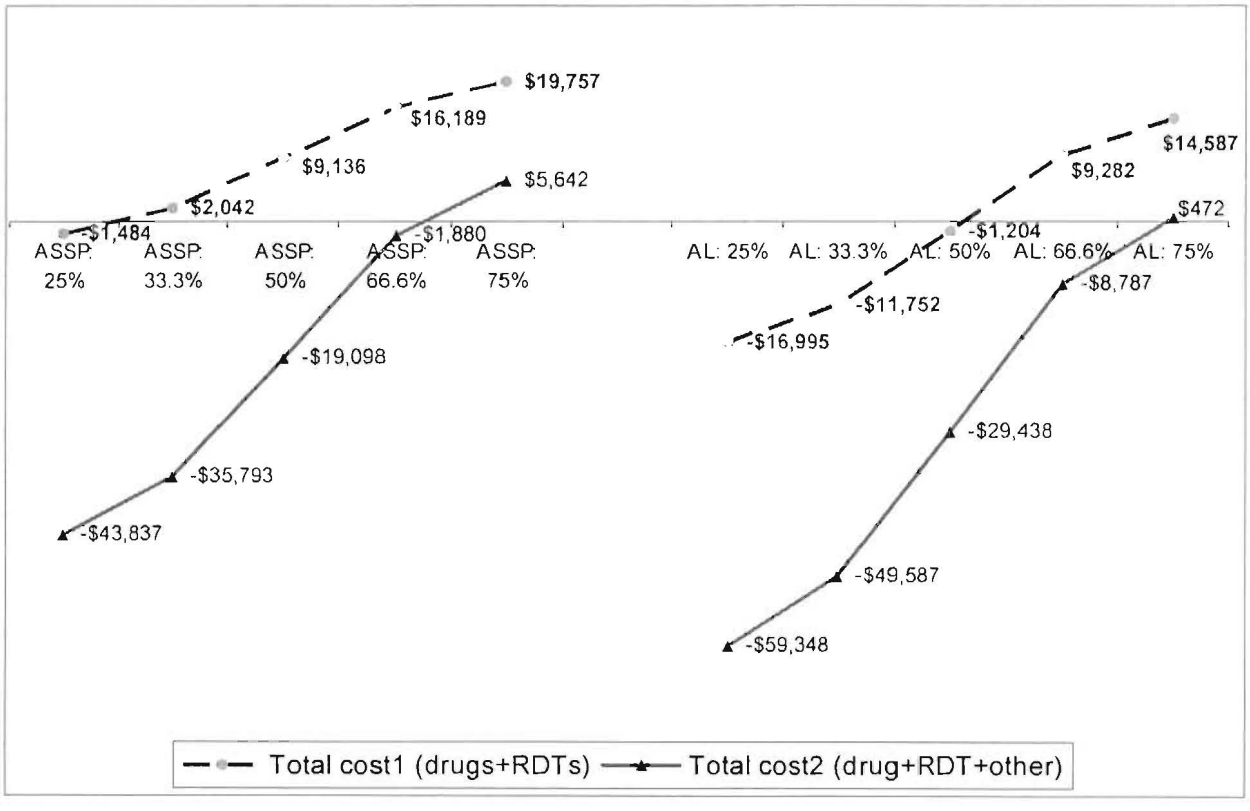
Results in Table 6.6 and Figure 6.4 compare two scenarios of *total costs;* that is (a) without and (b) with the inclusion of *other recurrent costs.* The inclusion of *other recurrent costs* (including costs of personnel, facility maintenance, utilities, etc) in the analysis (Table 6.4) obviously results in higher total costs of treatment. The difference in total costs is most notable for the clinical diagnosis option, where *other recurrent costs* comprise 47% and 57% of total costs when treating with artemether-lumefantrine and artesunate+SP respectively. It is interesting to note that "other recurrent costs" are higher than the cost of antimalarials for all the scenarios, when treating with artesunate+SP (see columns B and C in Table 6.6). With a relatively more expensive ACT (artemether-lumefantrine), the "other recurrent costs" are similar to the cost of antimalarials (see columns B and D in Table 6.6). These findings highlight that including "other recurrent costs" (and not just the cost of diagnosis and treatment) provides a more realistic picture of the real total costs of managing malaria patients.

Table 6.6: An overview of the various cost components for malaria diagnosis and treatment: Clinical vs. Definitive diagnosis (base case)

				Artesunate plus SP			Artemether-Lumefatrine		
RDTs (ALL fever cases tested)	No. of malaria cases	Cost of RDTs A	Other treatment costs B	Cost of antimalarials C	Total cost[1a] (A+C)	Total cost[1b] (A+B+C)	Cost of antimalarials D	Total cost[2a] (A+D)	Total costs[2b] (A+B+D)
Clinical diagnosis	32,023	$0	$56,472	$42,484	$42,484	$98,956	$63,048	$63,048	$119,520
If 25% fevers are +ve	8,006	$30,378	$14,119	$10,621	$40,999	$55,118	$15,762	$46,140	$60,259
If 33.3% fevers are +ve	10,664	$30,378	$18,637	$14,147	$44,525	$63,162	$20,995	$51,373	$70,010
If 50% fevers are +ve	16,012	$30,378	$28,238	$21,242	$51,620	$79,858	$31,524	$61,902	$90,140
If 66.6% fevers are +ve	21,327	$30,378	$38,403	$28,294	$58,672	$97,076	$41,990	$72,368	$110,772
If 75% fevers are +ve	24,017	$30,378	$42,357	$31,863	$62,241	$104,598	$47,286	$77,665	$120,021

Figure 6.4 presents a summary of the changes in the costs of routine RDT testing for all cases of suspected malaria before treatment, calculated on the basis of the two types of "total costs", that is, excluding and including 'other recurrent costs'. Results presented in Figure 6.4 show that when '*other recurrent costs*' are excluded from the analysis, the use of RDTs in all fever patients mainly results in **additional costs** when malaria cases are treated with AS+SP, except when 29% or less of all patients are malaria positive (i.e. when use of RDTs results in cost savings). However, the inclusion of *other recurrent costs* show that routine RDT use results in reduced costs as long as 69%, or less, of the patients tested are found to be positive and are treated with AS+SP. Similarly, for a relatively more expensive ACT (artemether-lumefantrine), when *other recurrent costs* are excluded, cost savings are realised only when about 52% or less are found positive and are treated with AL. When *other recurrent costs* are included in the analysis, there will be reduction in costs when up to 74% of the cases tested for malaria are found positive and are treated with AL.

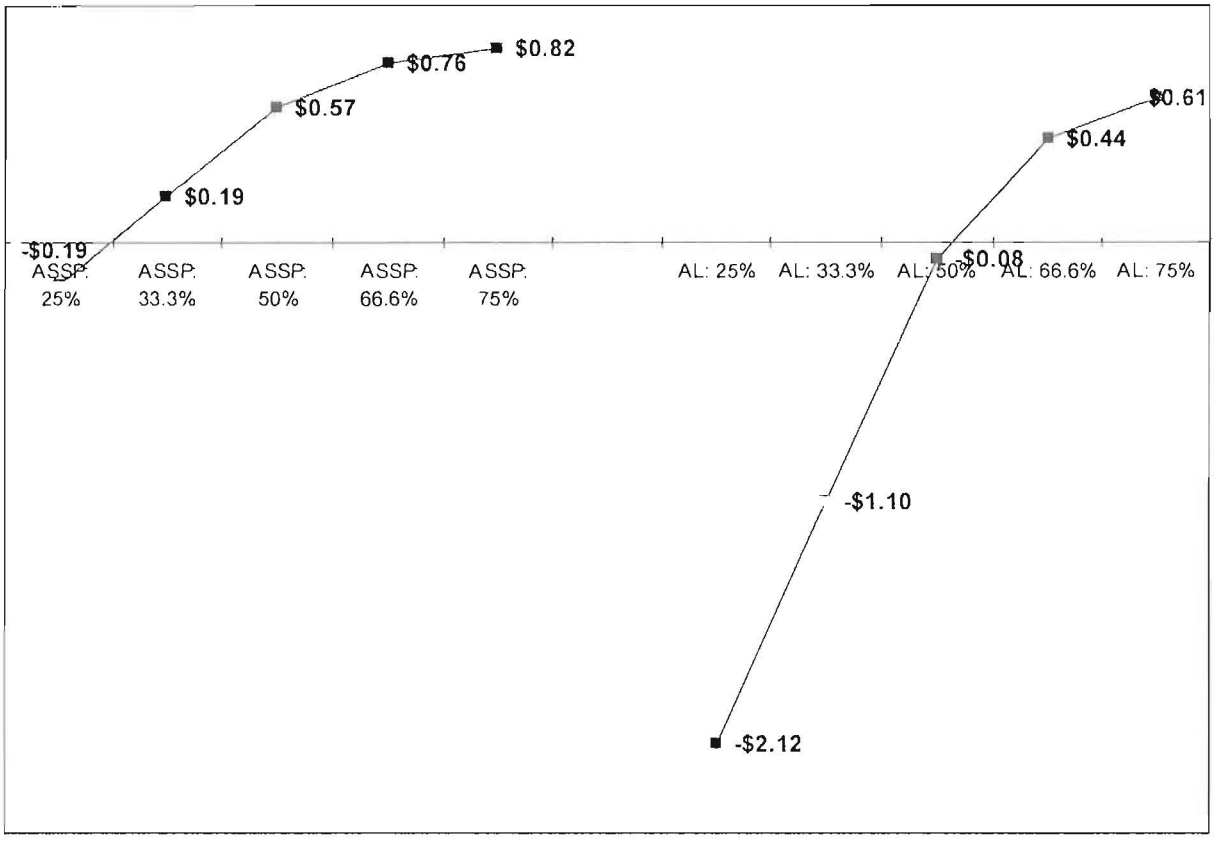
Figure 6.4: Incremental costs (calculated from different Total Costs) associated with use of RDTs in all fever cases (AS+SP vs. artemether-lumefantrine)



Note: The negative values show cost savings, while the positive values show additional costs.

Figure 6.5 presents results on the **incremental costs *per malaria positive patient treated*.** Incremental costs have been calculated using total cost of RDTs and antimalarials (excluding 'other recurrent costs') for the different scenarios. Results in Figure 6.5 again show cost saving (of $0.19 per patient treated) if malaria is present in under 29% of patients and that even when 75% of cases are malaria positive, the ***incremental cost*** *per malaria positive patient treated* is less than US$ 1, when AS+SP is used for treating malaria patients. On the other hand, when patients are treated using artemether-lumefantrine, there are ***cost savings*** *per malaria positive patient treated* of up to $2.12 (in the 25% scenario) as long as 52%, or less, of the suspected cases require treatment for malaria. Beyond the 52% cut-off point, additional costs are incurred with an ***incremental cost*** *per malaria positive patient treated* of up to $0.85 (when 95% of tested cases are found positive and treated with artemether-lumefantrine). According to the guideline provided by the Ad Hoc Committee on Health Research relating to Future Interventions Options, an intervention is considered to be "*highly attractive*" (hence 'cost-effective') in low income countries if it costs less than $25 per disability-adjusted life year (DALY) averted and any intervention that costs less than $150 per DALY averted should be considered "attractive" [194]. Although the health outcome used in this analysis is "number of patients treated" and not DALYs, this guideline could be helpful in determining whether an *incremental cost per malaria positive person treated* of less than $ 1 should be regarded as being highly cost-effective.

Figure 6.5: Incremental costs per malaria positive patient treated (base case): based on total costs of RDT and antimalarials; excluding 'other recurrent costs'.



Note: negative values refer to cost-saving per malaria positive patient treated

Sensitivity Analyses

One-way and multi-way sensitivity analyses were conducted to measure the effect, on the results, of changing:

(a) the prices of antimalarials,

(b) price of RDTs, and

(c) the age distribution of clinically suspected malaria patients, as follows;

Base case Age breakdown	for ASSP 28.3%; 15.3%; 56.4% and for AL 23.6%; 9.1%; 8.7%; 58.6%
Age breakdown 1	for ASSP 50%; 15%; 35% and for AL 45%; 9%; 9%; 37%
Age breakdown 2	for ASSP 40%; 20%; 40% and for AL 35%; 11.5%; 11.5%; 42%
Age breakdown 3	for ASSP 10%; 5%; 85% and for AL 5%; 4.5%; 4.5%; 86%

The results of the sensitivity analyses are presented in Figures 6.6 – 6.10.

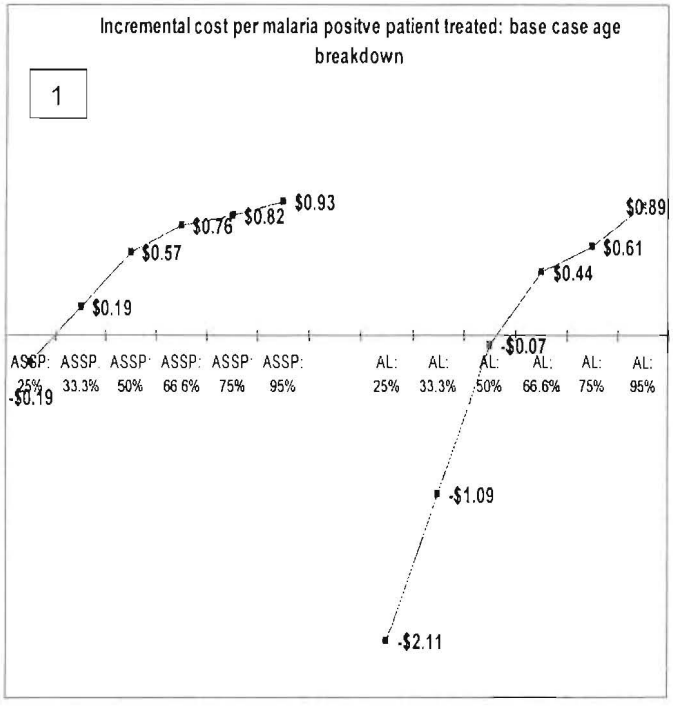
Sensitivity analysis on Age distribution (Figure 6.6 and 6.7)

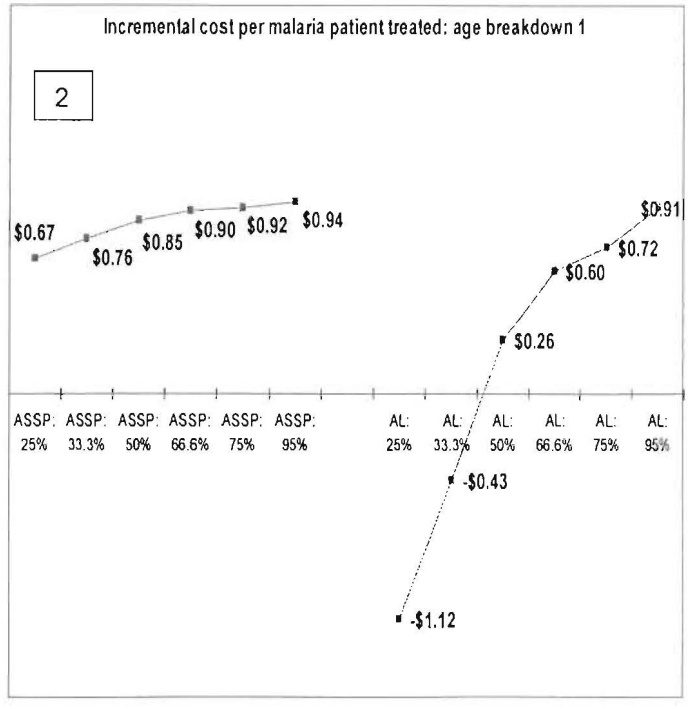
Results of the one-way sensitivity analyses show that changes in the proportions of suspected malaria cases in each group results in significant changes in the cost savings (or reduction in costs) and the related *incremental costs per malaria positive patient treated.* Results of the sensitivity analysis presented in Figure 6.6 reveal that when children make up a relatively larger percentage (e.g. 40-50% for AS+SP and 35-45% for artemether-lumefantrine) of the suspected malaria patients, the use of RDTs results in relatively higher additional costs and/or lower cost savings (see quadrants 2 and 3, i.e. age breakdown 1 and 2, in Figure 6.6). Note that when compared to the base-case scenario (quadrant 1), the curves in the graphs for age breakdown 1 and 2 shift upwards (Figure 6.6, quadrants 2 and 3). Similarly, the higher the percentage of adults among the suspected malaria cases (age breakdown 3), the lower the additional costs and the higher the costs savings (particularly with a relatively more expensive ACT like AL) associated with use of RDTs (Figure 6.6, quadrant 4). This finding is not surprising since the price of the ACTs for children is significantly lower than the price of the adult dose, and yet the price of the RDT remains constant for all age groups. Hence, having more young children to be tested and treated would be less cost-effective because one has to spend more money ($0.95) for a test in order to 'save' less money ($0.49 for AS-SP dose) if a child is found negative.

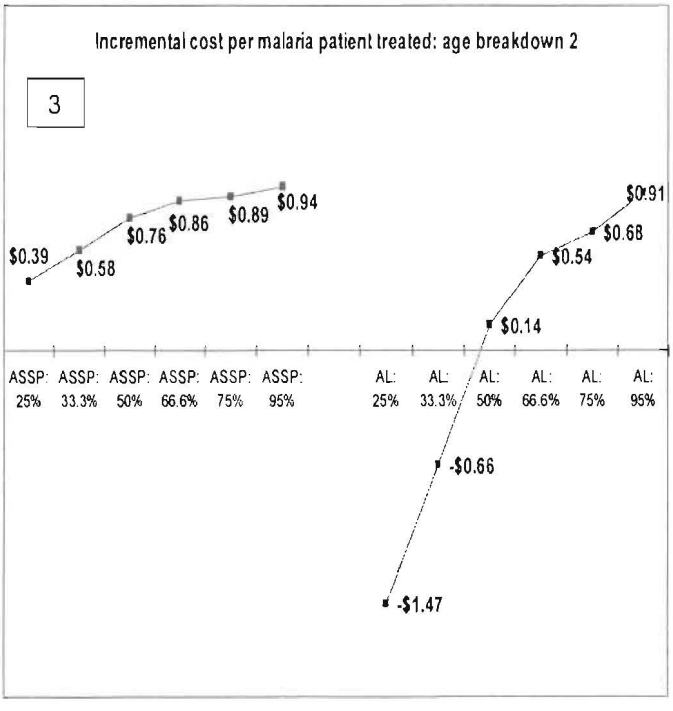
Results in Figure 6.7 show how changes in the age distribution of patients with fever (suspected malaria) have an impact on the decision between using RDTs in all fever cases and restricting their use to only those who are over 6 years of age. The higher the proportion of young children among those with suspected malaria, the more it makes economic sense to restrict the use of RDTs to those over the age of 6 years. For example, the results in the graphs for age breakdown 1 and 2 (Figure 6.7, quadrants 2 and 3), when compared to those in the base case scenario (Figure 6.7, quadrant 1), show that restricting the use of RDTs in patients over 6 years of age results in lower additional costs and/or higher costs savings (for both AS+SP and artemether-lumefantrine) (i.e. shift to the right of the

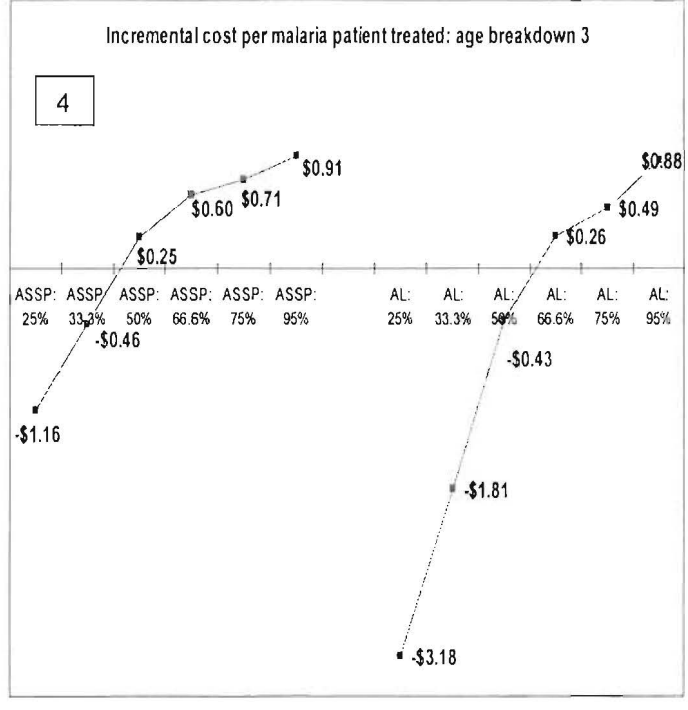
dotted line curve) when children make up a larger percentage of total fever cases. Similarly, when children under 6 years of age make up a very small proportion (e.g. 5-10% - age breakdown 3) of fever cases, although currently highly unlikely in any developing country, there is a small difference between using RDTs in all fever patients and restricting their use to only patients older than 6 years (Figure 6.7, quadrant 4). As mentioned above, the reason for this is mainly that the price of antimalarials for the 1-6 years age group is reasonably lower ($0.49 for AS+SP) or comparable ($0.9 for artemether-lumefantrine) to the price of one RDT ($0.95). Therefore, restricting the use of RDTs to patients older than 6 years is more cost-saving when children (6 years or younger) make up the greatest proportion – as they will be treated on a clinical basis and no RDT costs will be incurred for them. This result holds true especially where the price of antimalarials for the 1-6 years age group is reasonably similar to the unit price of RDTs (as is the case with artemether-lumefantrine). The more expensive the unit price of the antimalarial for the 1-6 years age group, relative to the unit price of RDTs, the lower the cost savings associated with restricting RDTs to patients over 6 years of age (Figure 6.7).

Figure 6.6: Impact of changes in age distribution of suspected malaria cases on incremental cost per malaria patient treated; excluding 'other recurrent costs'



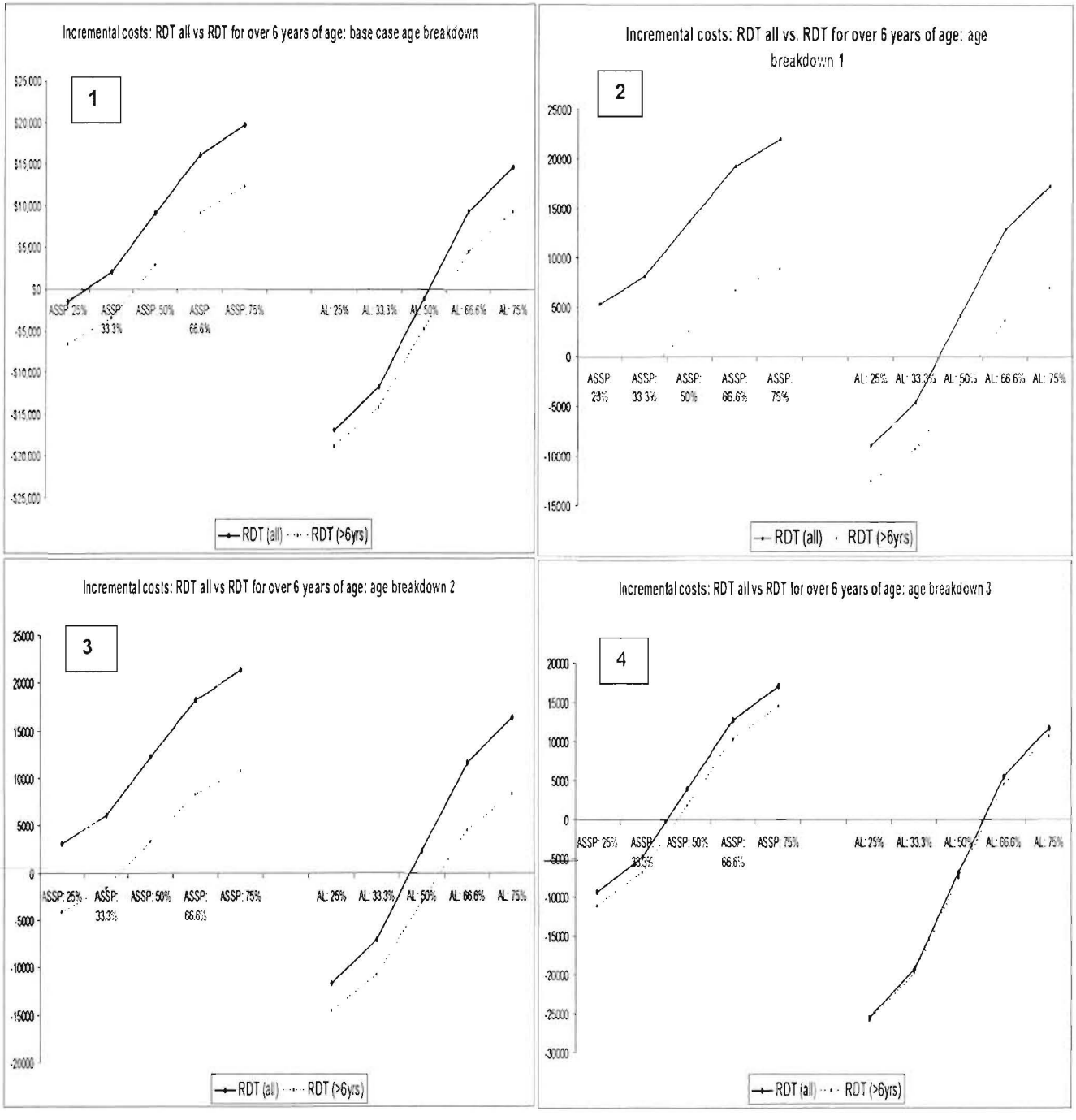






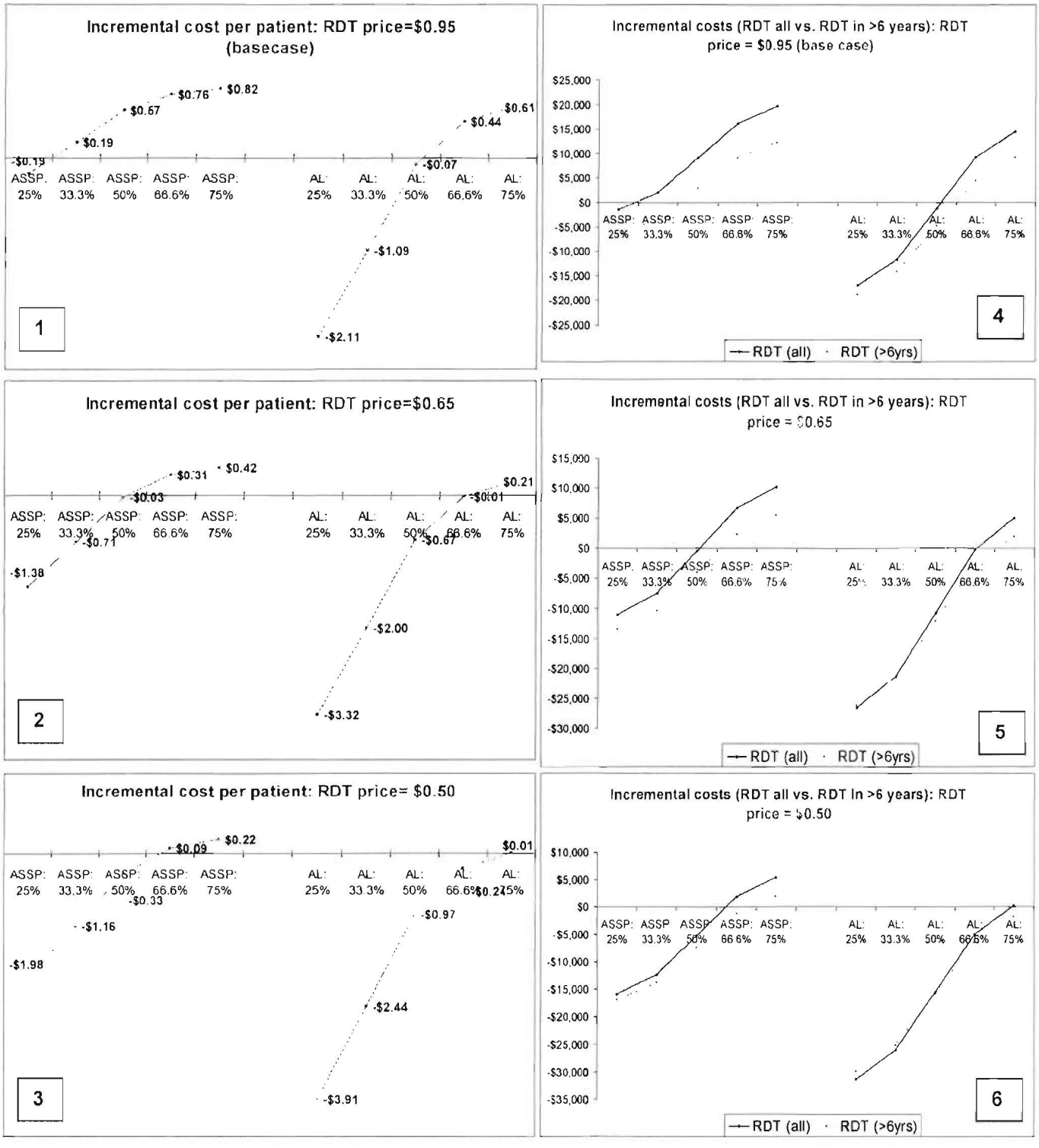
Base case Age breakdown	for ASSP 28.3%; 15.3%; 56.4% and for AL 23.6%; 9.1%; 8.7%; 58.6%
Age breakdown 1	for ASSP 50%; 15%; 35% and for AL 45%; 9%; 9%; 37%)
Age breakdown 2	for ASSP 40%; 20%; 40% and for AL 35%; 11.5%; 11.5%; 42%
Age breakdown 3	for ASSP 10%; 5%; 85% and for artemether-lumefantrine 5%; 4.5%; 4.5%; 86%

Figure 6 7: Impact of changes in age distribution of suspected malaria cases on incremental cost (RDTs + antimalarials); excluding other recurrent costs.



Base case Age breakdown	for ASSP 28.3%; 15.3%; 56.4% and for AL 23.6%; 9.1%; 8.7%; 58.6%
Age breakdown 1	for ASSP 50%; 15%; 35% and for AL 45%; 9%; 9%; 37%)
Age breakdown 2	for ASSP 40%; 20%; 40% and for AL 35%; 11.5%; 11.5%; 42%
Age breakdown 3	for ASSP 10%; 5%; 85% and for AL 5%; 4.5%; 4.5%; 86%

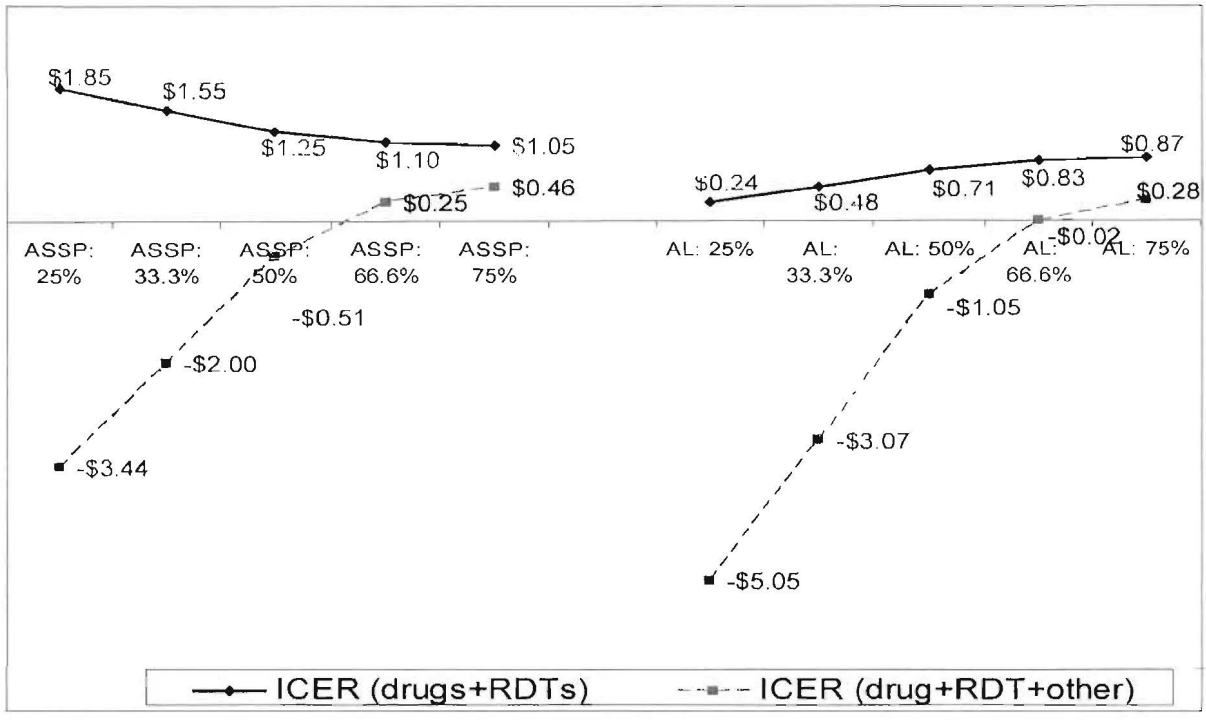
Figure 6.8: Impact of changes in price of RDTs on Incremental cost per patient treated and incremental costs ('other recurrent costs' are excluded from the analysis)



Sensitivity analysis on Unit Price of RDTs (Figure 6.8)

Results of the one-way sensitivity analysis on change of unit price of a rapid diagnostic test are presented in Figure 6.8. The lower the unit price of a rapid diagnostic test the more cost-effective it is to use definitive diagnosis (using RDTs) as the basis for ACT treatment, regardless of the price of the antimalarial being used for treating malaria patients. For example, when the price of an RDT is reduced from \$0.95 to \$0.50, the *incremental costs per malaria patient treated* reduces significantly from \$0.82 to \$0.22 and from \$0.61 to \$0.01 for AS+SP and artemether-lumefantrine, respectively, when prevalence of malaria is high (75% of the fever cases test malaria positive). Figure 6.8 also reveals that restricting the use of RDTs among patients older than 6 years only makes sense when the unit price of RDTs is relatively high. With a reduction in the unit price of RDTs from \$0.95 to \$0.50, limiting the use of RDTs in patients older than 6 years would result in significantly less economic gains (when patients are treated with AS+SP) and some economic losses in areas of low to moderate intensity malaria transmission (where 50% or less of fever cases are malaria positive and are treated with AL) (quadrant 6, Figure 6.8).

Figure 6.9: Impact of decrease in ACT prices on incremental cost per patient treated ('other recurrent costs' excluded from analysis)



Note: prices of antimalarials used for the one-way sensitivity analysis in Figure 6.9 are:

- SP price (per tablet): \$ 0.0257; AS price (per tablet) = \$ 0.077
- AL prices (full dose per age group): \$0.54, \$0.84, \$1.14 and \$1.44 (set arbitrarily at 40% less than base case prices).

Sensitivity analysis on ACT prices (Figure 6.9)

Figure 6.9 presents the one-way sensitivity analyses for decreases in the prices of ACTs. Results in Figure 6.9 show that the use of RDTs will be less cost-effective if the antimalarials being used for treatment are less expensive. This explains why, at least from an economic perspective, RDTs have not been widely used when the traditional and cheaper antimalarials, such as chloroquine or sulphadoxine-pyrimethamine monotherapy, were being used in areas of moderate to high intensity malaria transmission. However, when 'other recurrent costs' are included in the analysis, some cost savings would be obtained by routine use of RDTs as long as 60% and 67% of the fever cases are parasitaemic and are treated with AS+SP and artemether-lumefantrine, respectively (that is, at reduced ACT prices).

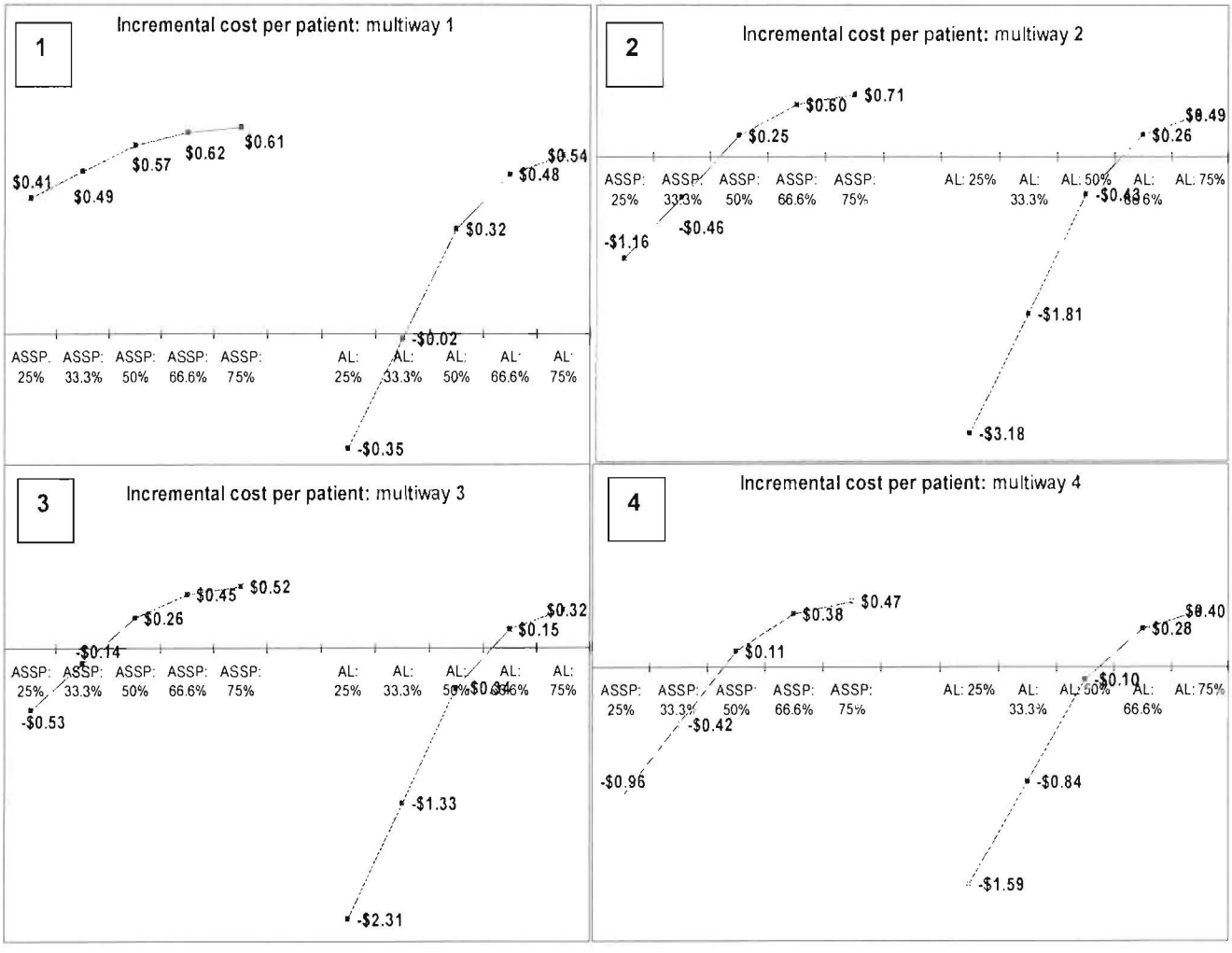
Multiway sensitivity analyses

Results of the multi-way sensitivity analyses are presented in Figures 6.10 – 6.12. In these analyses the prices of antimalarials, prices of RDTs and age distribution were varied to assess the effect of simultaneous changes in these variables (See above Table 6.5; Methods) on the earlier findings on cost-effectiveness of RDTs.

Figure 6.10 shows that, as expected, *multi-way 1* (high prices of ACTs and RDTs and children younger than 6 years taking up the highest proportion) is the context in which routine use of RDTs is least cost saving (for both AS+SP and artemether-lumefantrine) (quadrant 1, Figure 6.10). Regardless of the ACT used for treating patients, *multi-way 4* (i.e. low prices of ACTs and RDTs and the children younger than 6 years taking up a relatively small proportion of all fever cases) is the context in which RDTs are most cost saving / cost effective (quadrant 4, Figure 6.10). Results of *multi-way 2* sensitivity analysis show the impact of changing age distribution alone (without changing the prices of ACTs and RDTs), hence they are the same as those presented for *age breakdown 3* (Figure 6.5). In an area of high intensity malaria transmission (malaria prevalence of 75%) a comparison of the results of *multi-way 2* sensitivity analysis (Figure 6.10) with the base case results

(Figure 6.5) reveals that there is a decline in *incremental cost per patient treated*, for both AS+SP and artemether-lumefantrine, from \$0.82 to \$0.71 and from \$0.61 to \$0.49 for AS+SP and artemether-lumefantrine, respectively, purely as a result of changing the age distribution.

Figure 6.10: Multi-way sensitivity analyses: Incremental cost per malaria patient treated ('other recurrent costs' excluded)



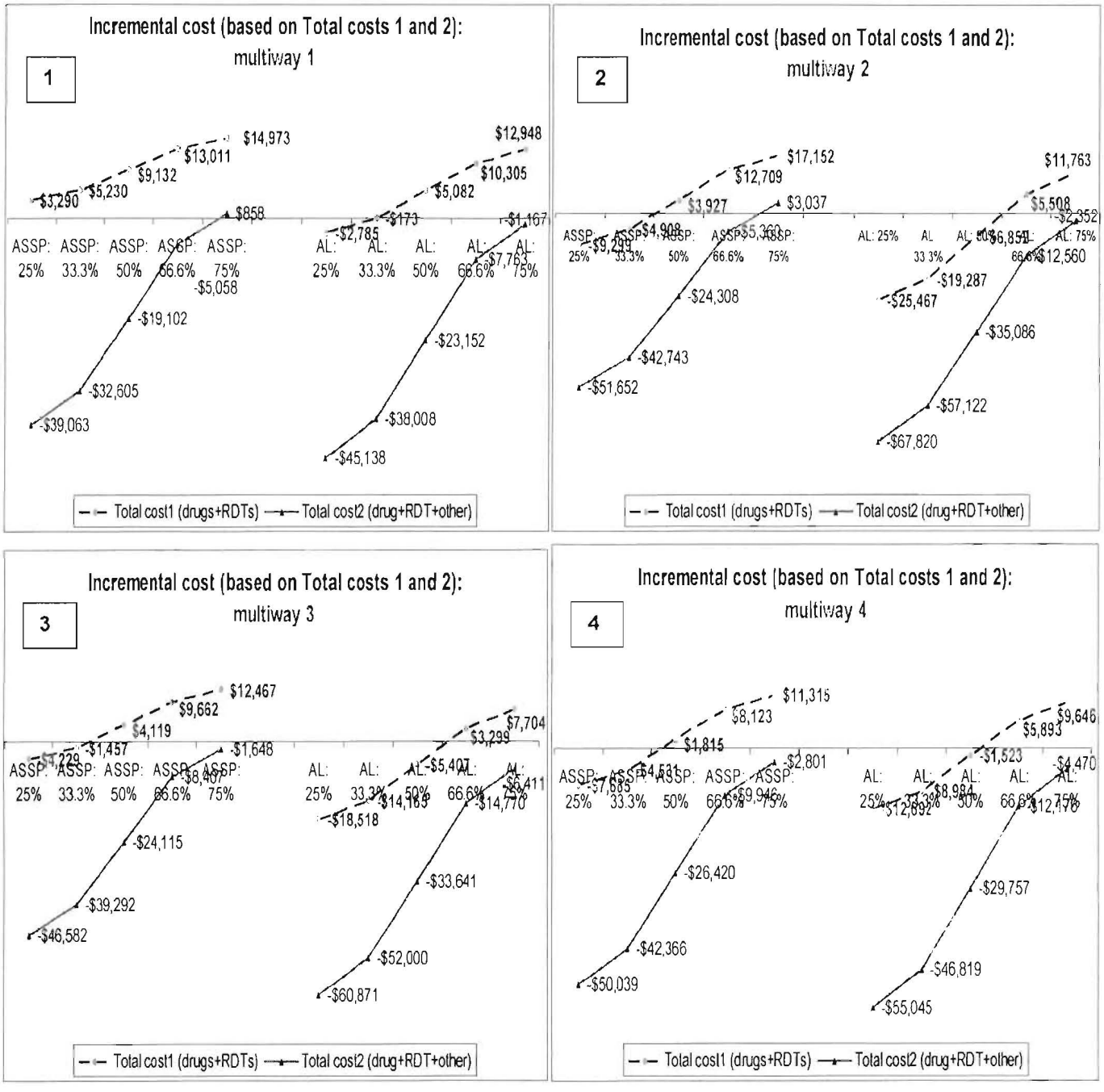
Results of *multi-way 3* sensitivity analysis (quadrant 3, Figure 6.10) show the impact of changing the price of RDTs and age distribution (without changing prices of ACTs). Results of *multi-way 3* sensitivity analysis, when compared with the *base case* results (see Figure 6.5), show that there is a reduction in the *incremental cost per malaria patient treated* (from \$ 0.82 to \$0.52 for AS+SP and from \$0.61 to \$0.32 for artemether-lumefantrine) when the proportion of fever cases who are younger

than 6 years of age reduces (*i.e.* from 28% to 10% for AS+SP and from 25% to 5% for artemether-lumefantrine), in an area of high intensity malaria transmission (where 75% of fever patients are tested malaria positive). The reduction in *incremental cost per malaria patient* remains regardless of the proportion of fever cases found to be malaria positive. Changes in costs are mainly due to the variations in RDT prices and the proportions of adults treated. As expected, the higher the proportion of suspected malaria cases in the adult age group (14+ years), the greater the cost savings. Variation in the prices of RDTs and antimalarials shifts the cut-off points at which definitive diagnosis results in cost savings. For example, when RDTs cost only $0.65 and the age distribution of patients presenting with clinical features of malaria is similar to our Mozambican population (i.e. *multi-way 4* sensitivity analysis), then RDTs are cost saving when up to 42% and 58% of fever patients require AS+SP and AL, respectively (quadrant 4, Figure 6.10).

These findings imply that even when the prices of ACTs remain at the levels used in the base case analyses, countries will benefit from using RDTs before providing ACT treatment, as long as RDTs are being obtained at or below a price of $0.65 and the proportion of children younger than 6 years among the fever cases is similar to or smaller than the Mozambican sites studied.

Figure 6.11 shows the results of the multiway sensitivity analyses with and without the inclusion of "other recurrent costs". Figure 6.11 shows that greater cost savings are obtained when "other recurrent costs" are included in the analysis, compared to when they are excluded. This is true for all multi-way sensitivity analyses scenarios (see quadrants 1 – 4, Figure 6.11). Furthermore, Figure 6.11, shows that the inclusion of "other costs" results in greatest costs savings are achieved with *multi-way 1* and *multi-way 4* (see quadrants 1 and 4, Figure 6.11), when prices of antimalarials and RDTs are set to the lowest possible and when the biggest proportion of suspected malaria cases are over 6 years of age.

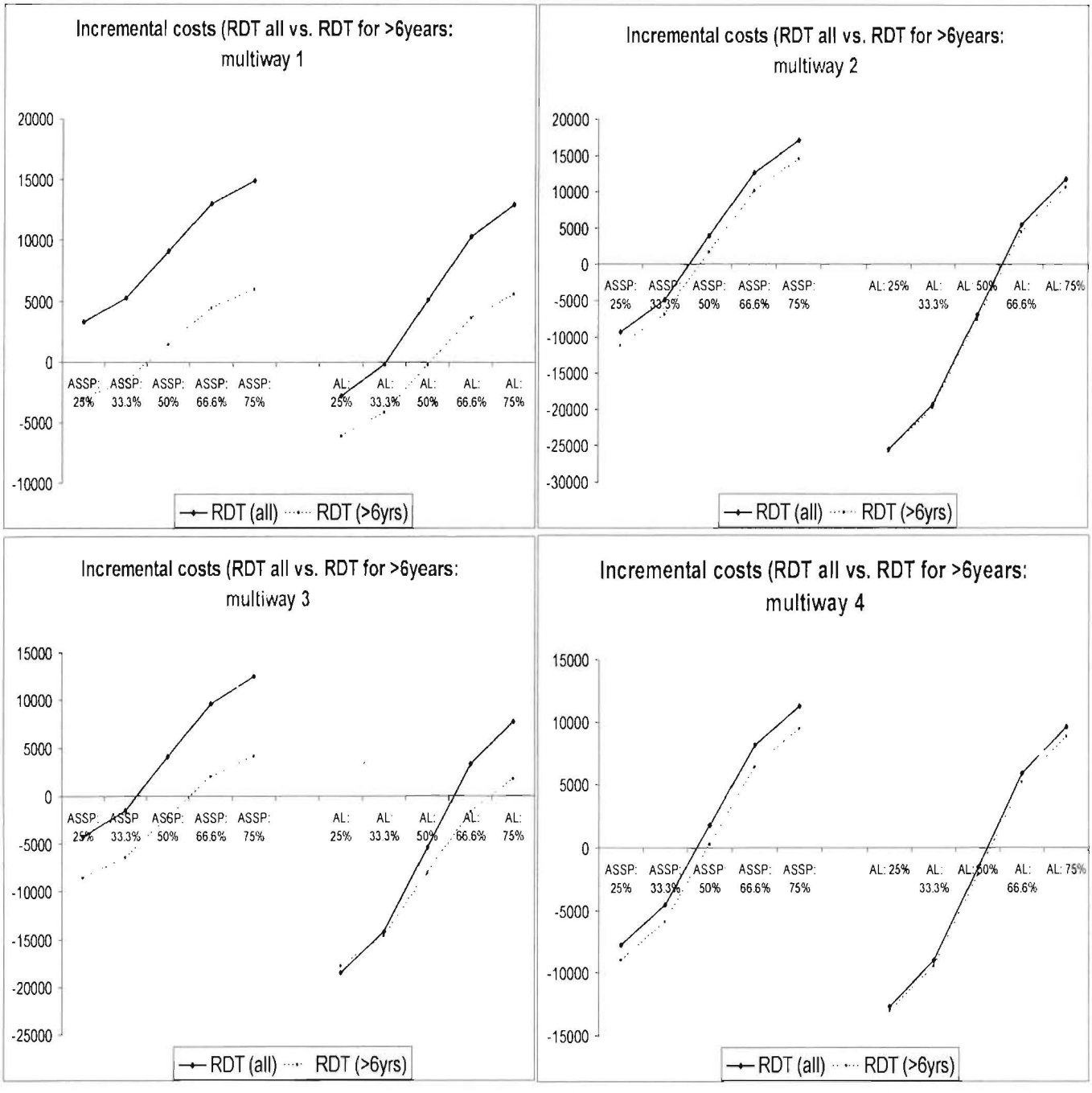
Figure 6.11: Multi-way sensitivity analyses: Incremental costs (based on total costs with and without 'other recurrent costs').



Note: Positive values represent the additional costs while the negative values represent cost savings made.

Results of *multi-way sensitivity analyses 2 and 4* (Figure 6.12) confirm the finding that the option to restrict RDT use to fever patients older than 6 years does not make economic sense when children 6 years or younger constitute a small proportion of fever cases tested and/or when the unit price of RDTs is lower than the unit price of antimalarials for treating children younger than 6 years.

Figure 6.12: Multi-way sensitivity analyses: incremental costs (RDT all vs. RDT for >6 years) – excludes other recurrent costs



Note: The positive values represent the additional costs incurred while the negative values represent cost savings made.

6.4: LIMITATIONS OF STUDY

In the analyses presented in this chapter, the prices of RDTs and ACTs were based on final costs to the public sector provider and are thus inclusive of taxes, and shipping and transport costs. The focus of the analyses in this chapter is limited to the evaluation of costs, cost savings and/or incremental costs related to using RDTs as part of routine management of all suspected malaria cases as the basis for prescribing ACT malaria treatment.

A full economic evaluation of RDTs, therefore, is beyond the scope of the analyses in this chapter since results do not include the costs and benefits resulting from the consequences of avoiding over-diagnosis. For example, this study is only focused on the treatment of malaria patients and does not assess the other benefits associated with the use of RDTs, such as minimising the delays (and associated costs) in providing appropriate treatment for those who are malaria negative, who would have otherwise been inappropriately treated with antimalarials. This improved use of antimalarials would limit drug pressure and so should delay antimalarial resistance. Another added benefit of using RDTs, not captured in the analyses presented, is that of identifying malaria cases that would have otherwise not been identified through clinical diagnosis (e.g. the false negatives) and providing them with prompt antimalarial treatment. In the absence of definitive diagnosis, misdiagnosis of malaria would result in increased morbidity costs (i.e. treatment seeking and hospitalisation costs) and sometimes death (mortality costs).

One of the disadvantages of RDTs is that they cannot quantify parasite density. Also they remain positive for weeks after parasite clearance and most only identify falciparum and not other species of malaria. Analyses taking into consideration issues of sensitivity and specificity or the quality of RDTs were beyond the scope of this study. Instead, the analyses in this chapter assume 'true positives' and 'true negatives'; the RDTs used in this study were reported to have high sensitivity (100%) and specificity (96.2%) [89].

One of the limitations of this study is that it limits itself to studying the cost-effectiveness of the concurrent use of RDTs together with the use of expensive antimalarials (specifically ACTs) at pilot

level. Data from pilot sites does not include the cost of wide-scale implementation of both ACTs and RDTs. In most countries, such costs are likely to be relatively high and could have the potential of eroding the cost savings resulting from improved diagnosis and more rational use of antimalarials.

Further, in the absence of real data on quantity of antimalarials consumed, this study assumes that all patients with malaria are always treated with the correct antimalarial and dosage. While this might be largely true in a pilot programme, it might not always be true in most malaria endemic areas (especially in Africa) where health facilities are inadequately staffed and where there are shortages or stock-outs of antimalarials.

The most important limitation of this study is that it assumes that both health care workers comply with limiting ACT treatment to only those cases that are confirmed malaria positive. Patient pressure and poor availability of treatments for non-malaria febrile illnesses could result in RDT negative patients still being treated with ACTs. Extensive training and on-site supervision is needed to ensure compliance of health care workers.

6.5: DISCUSSION AND CONCLUSIONS

The findings of this study show that the introduction of RDTs is likely to be cost saving when ACTs are implemented, particularly in areas of low-moderate intensity malaria transmission and/or if all costs related to malaria treatment are taken into account. This result holds even when relatively inexpensive ACTs are used, but the higher the price of the ACT, the greater the cost savings from introducing definitive diagnosis. The finding that drug cost-savings are higher in low transmission areas was also reported by Goodman and others [27]. This is because in low transmission areas a higher proportion of malaria cases are adults who require a higher antimalarial dose. This effect results in higher malaria prevalence cut-off point at which RDTs are cost effective. For example, limiting artemether-lumefantrine use to only confirmed malaria cases is cost saving until more than 74% of patients test positive when '*other recurrent costs*' are included in the analysis, compared with 69% when these other recurrent costs are excluded. A number of studies indicate that many countries in Africa are likely to have actual Pf prevalence of well below 67% of all patients who would be

clinically diagnosed as malaria. A recent study in Uganda, an area of high intensity malaria transmission, found that only 57% of those who were clinically diagnosed as having malaria were actually parasitaemic [186]. From the findings of several studies undertaken separately in 15 countries presented by Amexo and others, on average there is an overestimation of malaria cases of 39% (lowest 4% - highest 72%) when clinical diagnosis is used in children under 5 years of age [7]. On the other hand, clinical diagnosis may fail to pick up some patients who actually have malaria. Luxemburger and others found that none of the malaria symptoms alone or in combination proved to be a reliable predictor of malaria. They report that at best clinical diagnosis would result in prescription of antimalarials in 29% of the non-malaria febrile illnesses and 49% of the true malaria cases (suggesting that 51% of the infections would go untreated initially) [59].. It is important to note that one of the issues around the use of RDTs is that they are unlikely to be used if malaria is not clinically suspected and so will not address the problem of false negatives arising from clinical diagnosis.

Findings of this study show that as long as the unit price of RDTs is similar to or greater than the unit price of antimalarials for treating a child 6 years or younger, restricting the use of RDTs to patients older than 6 years is more cost saving and/or cost-effective than using RDTs in all fever patients. This is particularly true when children 6 years or younger make up the biggest proportion of fever cases. Furthermore, in a community with higher intensity malaria transmission – this is the age group at highest risk of severe malaria as young children are less likely to have acquired partial malaria immunity.

Furthermore, findings highlight that including "*other recurrent costs*" (and not just the cost of diagnosis and treatment) provides a more realistic picture of the real total costs of managing malaria patients. This is true because regardless of the number of malaria cases some overhead costs (such as personnel, maintenance of buildings, and others) have to be incurred. Findings from the results presented in this chapter show that RDTs are cost-saving, even from a narrow perspective when only diagnostic costs and cost of antimalarials are considered. Results however show that RDTs become even more cost-saving and cost-effective when a wider perspective of costing is considered, that is to include other recurrent costs. However, as the Ministry of health will still incur these other recurrent costs, whether they are allocated to malaria or to other diseases, policy makers may be more strongly

influenced by the narrow perspective that excludes these other recurrent costs.

With improvements in malaria control and higher costs of antimalarial treatment, there is increased opportunity for saving costs through the introduction of rapid diagnostic tests in facilities and/or communities where microscopic confirmation of malaria diagnosis is not reliably available [195]. Amexo and others suggest it is unethical to continue with high levels of malaria misdiagnosis in light of the introduction of expensive antimalarials and availability of cost-effective methods of diagnosing malaria (such as RDTs) [7]. This argument in favour of limiting antimalarial use to confirmed cases is strengthened by considering the enormous effect of drug pressure on antimalarial resistance. An equally important reason for limiting antimalarials to those with the disease is the potential for side effects, the nature and severity of which have not been well documented in African populations.
Provided that rapid diagnostic tests with high sensitivity and specificity are available at below $0.65 per test, this intervention would be cost saving for populations with a similar age distribution to those studied in southern Mozambique, provided these results limit AS+SP (or AS+AQ) use to fewer than 52% of clinically diagnosed malaria cases. Cost savings are greater if the ACT in use is more expensive (e.g. Artemether-lumefantrine) or if the symptomatic population has an older age distribution. Similar findings are reported by Rolland and others where the cost-effectiveness of RDTs is studied in the context of malaria epidemics. They report that RDTs would be cost-effective at a malaria prevalence up to 45% when AS+AQ is used for treatment and up to 68% when artemether-lumefantrine is used [196]. In this era where the use of ACTs is being globally encouraged and even financed, strategies such as the concurrent use of ACTs and RDTs should be equally encouraged and financially supported.

It is also important to highlight the fact that even in situations where RDTs are not cost-saving, they could be cost-effective if their use leads to significant improvements in health outcomes. While there is limited evidence to demonstrate this [27], it is possible that the use of RDTs might lead to improved management of non-malaria cases. This depends on health workers and patients being willing to accept a negative malaria test result and on healthcare workers being able to accurately diagnose and treat non-malaria fevers. In addition, more appropriate use of antimalarials (resulting from restricting them to only those who are confirmed to have malaria) could reduce the spread of drug resistance.

Lastly, there is need for more economic evaluation studies of the concurrent introduction of RDTs together with ACTs, particularly for more wide-scale implementation at national level rather than at the district level, as was the case in this pilot study. Preferably such evaluation studies should be comprehensive enough to measure and include in the analysis the cost of wide scale implementation of RDTs and ACTs, and also the costs of treating non-malaria fever patients [197]. Although of critical importance in RDT selection, the assessment of the specificity and sensitivity and field suitability of the RDTs used were beyond the scope of the analyses presented and discussed in this chapter. However, it is recommended that future studies include these aspects of evaluating RDTs.

In conclusion, rapid, accurate and accessible detection of malaria parasites has an important role in addressing the problem of malaria over-diagnosis and inappropriate use of antimalarial drugs. RDTs offer the potential to provide accurate diagnosis to all populations at risk, particularly those unable to access good quality microscopy services. In the context of use of expensive antimalarial drugs such as ACTs, RDTs can be cost-saving and cost-effective depending on the prevalence of malaria parasites, the price of RDTs, price of antimalarial drug being used for treatment and the age distribution of clinically diagnosed malaria patients.

7. DISCUSSION

7.1: INTRODUCTION

Despite all the research and control efforts that have gone into reducing the burden of malaria, it remains a major public health and economic burden in most tropical countries. The eradication of this complex disease has become difficult because it involves the dynamics of three parties: the vector mosquito, the parasite, and the human host. Today's biggest challenge to malaria control is the development of resistance, by vector and parasite, to insecticides and cheap antimalarial drugs [198]. Nosten and Brasseur note that dealing with the spread of antimalarial drug resistance is indeed the most urgent and difficult task ahead, and they advocate for the invention of new approaches to malaria control and the abandonment of the old ones and recommend that as a minimum, governments of malaria endemic countries need to continuously monitor and assess the effectiveness of current first-line drugs [198].

Malaria control becomes more effective when several strategies are in place so as to work together to reap a stronger synergistic impact on reducing the malaria burden. This means that it is better to deploy strategies that tackle each of the 3 key factors that are responsible for the transmission of the disease (i.e. the vector, the parasite and the human host). A multifaceted approach to malaria control that includes vector control (through widespread indoor residual insecticide spraying and use of insecticide treated bed nets), improved malaria diagnosis (through the use of definitive diagnosis) and prompt, accessible and effective malaria case management is likely to have a much higher impact and better benefits than just having only one of these approaches on its own. Such a broad approach to malaria control provides a more comprehensive way of containing the transmission of malaria and the related implications. On one hand, while an effective IRS strategy may not completely eradicate the vectors responsible for the transmission of malaria, it greatly reduces the number of mosquitoes and hence minimises the potential number of infective bites (thus minimising malaria transmission) On the other hand, having accurate, easy-to-use, rapid and accessible definitive diagnostic tools enables quick diagnosis for malaria. This not only promotes rational use of antimalarials (by restricting

their use to only those who need them), but it also allows for patients whose fever episodes are not caused by malaria to receive timely appropriate treatment. Lastly, having a highly effective first line antimalarial drug that is easily accessible (both physically and financially) – particularly one that has attributes of high cure rates and reduction of gametocytes – reduces the number of treatment failures (and recrudescence and progression to severe malaria) and the associated morbidity and mortality costs. South Africa has benefited greatly from having such a multi-prong approach to malaria control in place over an extended period of time.

On the strategy of providing prompt and effective treatment, as a response to the wide-spread antimalarial drug resistance, the use of combination therapy, particularly artemisinin-based combination antimalarials are now strongly recommended. The use of ACTs offers a unique combination of rapid and improved cure rates, delayed or reduced emergence of resistance to the drug components of the combination, as well as the potential for reducing transmission of the disease [2, 3, 26, 198-201]. Following common sense, it is absolutely essential that these very few remaining effective antimalarials are used rationally and optimally [198]. However, the effective deployment of ACTs in Africa – with high intensity malaria transmission, severely constrained health care systems and lax and ineffectual regulations on pharmaceuticals' sale and use – remains complicated. As noted by Bloland and others, it is not enough for these ACTs to exist, but they must be affordable, available, accessible and acceptable by the end user, who should be able to take them in correct dose and duration of therapy [199]. In addition, they highlight an important issue that these ACTs should be "*robust enough in terms of their ability to withstand the misuse that is likely to occur and the selective pressure that this misuse will place on the parasite*" [199, p. 3765]. Further, it is recommended that ACT should be co-formulated or at least co-packaged to improve compliance and minimise the use of monotherapy.

Linked to the issue of rational use of antimalarials is the fact that most cases of fever (or uncomplicated malaria) are managed outside the formal health sector, on the basis of clinical diagnosis, using antimalarial drugs purchased from various places including drug shops, shops, kiosks and drug vendors and occasionally private pharmacies [199, 200]. In the quest to bring antimalarials as close to the home as possible, the home-based management of malaria strategy was

recommended to endemic countries as a way of providing prompt treatment, especially in countries with inadequate and poor access to health care facilities. While this strategy has obvious advantages in reaching the Roll Back Malaria goal of 'prompt treatment', it has opened up a debate on whether the more expensive ACTs should be made available at community level [200]. Notable issues for consideration on this matter include:

- ★ the potential channelling ACTs through the home-based management of fever strategy to increase drug pressure and accelerate the development of resistance to ACTs, resulting from un-regulated use of the drugs, which will be a real disaster that would leave management of the disease in a crisis;
- ★ the emergence of resistance to these precious drugs would be facilitated by the lack of definitive diagnostic tools at community level (and even in the formal health sector facilities), resulting in over-diagnosis of malaria. This would mean that substantive amounts of ACTs will be taken by those who actually do not need them. This unchecked use of drugs is not cost-effective.

Findings of the studies conducted in Kwazulu Natal and Mpumalanga (South Africa), presented and discussed in chapters 4 and 5, have shown that artemisinin-based combination antimalarial drugs are not only cost-effective, but also cost-saving in the South African context. Factors contributing to the cost-effectiveness of ACTs in this context include:

- ★ The existence of established effective vector control interventions through IRS, which has optimised ACTs' impact on transmission of malaria;
- ★ The treatment policy in place before the deployment of ACTs (i.e. SP monotherapy) was particularly prone to rapid development of resistance (as evident following prolonged use of SP in Kwazulu Natal). Even in the instance where SP monotherapy still has high cure rates (as was the case in Mpumalanga), it is often associated with very high gametocyte carriage which fuels malaria transmission. Therefore, an antimalarial that combines the attributes of high cure rates and reduction of malaria transmission (e.g. ACTs), when compared with SP monotherapy, is considered ideal both from a public health and economic perspective.
- ★ High coverage with ACTs (within the study sites) was achieved within public health facilities and given the reasonably good access to public health facilities and the very limited reliance

of care in private and informal sectors (particularly in the study sites which were largely rural), the impact of ACTs on malaria transmission was optimised.

- ★ As shown by the findings of the household surveys, there was a reasonably good degree of adherence by patients to the completion of the antimalarial course of treatment. This has enhanced the ACTs' cure rates and delays the onset of resistance to the drugs.
- ★ The high costs of managing malaria patients in South Africa, particularly at inpatient level in Mpumalanga, resulted in relatively high cost savings for every malaria cases averted.
- ★ Routine use of definitive diagnosis in the South African study sites has resulted in limiting ACT use to those who need them. This has resulted in reduced costs of managing malaria patients (in terms of both the cost of antimalarials and the other recurrent and capital costs associated with treating malaria patients).

The established routine use of definitive diagnosis has enhanced the cost-effectiveness of ACTs in the South African study sites. Routine use of definitive diagnosis may also have contributed to the sustained high SP cure rates (90%) in Mpumalanga 5 years after use as first line treatment; in Malawi, where malaria diagnosis is clinical and intensity of transmission moderate to high, SP cure rate was only 38% after 5 years as first line malaria treatment policy [202]. Given the critical relevance of definitive diagnosis to the cost-effectiveness of antimalarial drugs, the study of costs of malaria management, and in particular the evaluation of the cost-effectiveness of introducing definitive diagnosis was conducted in southern Mozambique. Findings from this study have shown that malaria prevalence, age distribution of suspected malaria cases and prices of ACTs and RDTs are important determinants of cost-effectiveness of RDTs, and are discussed further in Section 7.3 below.

7.2: COST AND COST-EFFECTIVENESS OF ANTIMALARIAL DRUGS IN THE CONTEXT OF EFFECTIVE VECTOR CONTROL IN SOUTH AFRICA

From the 1995/96 malaria season to 2000, there was an alarming increase in the number of malaria cases notified in South Africa (64,622 in 2000), with a disproportionate increase in Kwazulu Natal when compared with the other malaria provinces in South Africa (see Fig 5.1). About 65% and 19% of the notified cases in 2000 originated from Kwazulu-Natal and Mpumalanga respectively.

Resistance to first line treatment (SP) was mainly prevalent in Kwazulu Natal. Although climatic changes may have played a role in Kwazulu Natal, pyrethroid resistance in the vector and the high level SP resistance prevalent in *P. falciparum* are believed to have been responsible for this dramatic increase. By 2000 the notified malaria case fatality rate in Kwazulu Natal was 8.1 deaths per 1000 cases, compared with 3.6 per 1000 in Mpumalanga where SP remained highly effective. Several strategies were implemented to reduce this burden of malaria. Following the changes in the IRS strategy in Kwazulu Natal, the introduction of IRS in southern Mozambique and the change in treatment policy from SP monotherapy to ACTs in both Kwazulu Natal and Mpumalanga, there were great reductions in the malaria burden in both Kwazulu Natal and Mpumalanga. The total number of malaria cases notified in Kwazulu Natal province reduced by 94% from 41,786 in 2000 to 2,345 in 2002, while a 36% reduction in malaria notifications was noted in Mpumalanga over the same period. A further 46% reduction in malaria notifications was noted between 2002 and 2003 in Mpumalanga. Death notifications in Kwazulu Natal and Mpumalanga decreased by 95% and 33%, respectively, between 2000 and 2002. A further 47% reduction in death notifications in Mpumalanga had been achieved by the end of 2004.

The remarkable improvements in malaria control and public health in Kwazulu Natal reflect the combined effect of indoor residual insecticide spraying with an effective insecticide in both Kwazulu Natal and southern Mozambique, and the replacing of SP with an effective ACT (artemether-lumefantrine) as the first line treatment of uncomplicated malaria. Apart from the change in treatment policy from SP monotherapy to AS+SP, there were no changes in vector control strategies in Mpumalanga. However, there might have been some spill-over impact of IRS in southern Mozambique that might have enhanced the reductions in malaria cases and deaths in Mpumalanga. The change in malaria first line treatment policy to AS+SP, however, has clearly resulted in improvement in health outcomes between 2003 and 2004.

Findings of the economic evaluation studies in Kwazulu Natal and Mpumalanga show that both AL and AS+SP are cost-saving relative to SP monotherapy. This means that the change from SP monotherapy to AL and AS+SP, in Kwazulu Natal and Mpumalanga, respectively, resulted in a reduction in overall costs of treating malaria patients. This finding remained true even when sensitivity

analyses of key variables were performed. For example, even when the most conservative estimates (25%) of the relative contribution of AL to the decline in malaria cases was used, and when the highly inflated prices of SP paid by Kwazulu Natal are replaced with international median prices, AL was still cost saving as well as cost-effective in the Kwazulu Natal setting. It can be argued that since a before-and-after approach was used, there might be other 'confounding factors' whose impact has not been assessed, such as change in climate in the region. It is important, however, to note that as discussed previously in the methods sections other confounding factors are unlikely explanations for the changes observed in both study sites, as there were no changes in the health care systems and the malaria control programmes, and the climatic changes were not substantial (Delphi Survey results). Moreover, the results presented for Kwazulu Natal (in chapter 4) include possible scenarios where such factors have been taken into consideration (based on the Delphi estimates). Results show that ACTs remain cost-saving and cost-effective even when the possible contribution of these factors is taken into consideration. On the basis of this, it can be argued that the findings on cost-effectiveness of ACTs presented in this thesis are plausible. Although there was no control study site in Kwazulu Natal (i.e. where ACTs were not introduced), Mpumalanga could be regarded as a 'control study site' with respect to the key confounding factors (of changes in IRS, as previously discussed) in Kwazulu Natal. Therefore the comparison between Kwazulu Natal (where there were more obvious confounding factors) and Mpumalanga is sufficient to demonstrate that the findings presented on cost-effectiveness of ACTs (from both Kwazulu Natal and Mpumalanga) are plausible in areas with effective vector control. In addition, adequate sensitivity analyses were undertaken for KZN using the Delphi estimates. Similarly, results from Price and others (Lancet, 1996) and Nosten and others (Lancet, 2000) confirm the plausibility of our findings of the substantial effective of ACTs in reducing malaria case numbers.

The cost-savings presented in this thesis are those achieved from reduction in costs for malaria outpatients (i.e. uncomplicated malaria) and reduction in costs for malaria inpatients (i.e. severe malaria). Including changes in inpatient costs in the analysis of cost savings is due to the fact that only severe malaria patients are hospitalised and that the occurrence of severe malaria is mainly related to the failure of first line treatment. Thus, it is appropriate to attribute cost savings from reductions in inpatient care to the introduction of ACT. However, there are other factors that predispose patients with uncomplicated malaria progressing to of severe malaria may change (e.g.

delay in treatment seeking, host risk factors such as pregnancy or infancy and that certain parasite genotypes are more pathogenic). Nevertheless, these other possible changes would be unlikely to change markedly in the relatively short period of this study.

The evaluation of the validity of the Delphi estimates obtained in this study is difficult since there are no other methods of disaggregating the impact of the three malaria control interventions, implemented in rapid succession, in Kwazulu Natal. In general, there are several factors that influence changes in malaria prevalence in any given area, including among others, changes in climatic conditions, changes in species and level of insecticide resistance of malaria vectors, the species of malaria parasites being transmitted within a population in a specific area, the extent to which there are cross-border activities in neighbouring areas, the degrees of malaria prevalence in those neighbouring areas, the nature of malaria control initiatives in neighbouring areas, as well as the effectiveness of the antimalarials used in the management of malaria. Although the three malaria control initiatives (namely: reintroduction of DDT in Kwazulu Natal, introduction of IRS programme in southern Mozambique and change in malaria treatment policy from SP to AL) are all considered to have contributed to the marked reduction in malaria cases, admissions and deaths in Kwazulu Natal, one cannot completely rule out the influence of other factors, such as climatic changes.

Comparing the trends in malaria cases and deaths in Kwazulu Natal (where there were 3 interventions) with those in Mpumalanga (where there was 1 intervention), was helpful in interpreting the reliability of the estimates derived from the Delphi survey, of the contribution of artemether-lumefantrine in Kwazulu Natal. The marked decrease in malaria cases and admissions in Mpumalanga after the introduction of ACTs, without any changes to local vector control programmes, suggests that the median estimates of the Delphi survey were underestimates. Possibly, the upper limit estimates, which still provide a lower percentage reduction than that in Mpumalanga, are more accurate in capturing the contribution of artemether-lumefantrine to reduction in malaria prevalence. As far as the research question is concerned, however, importance should be placed more on whether or not artemether-lumefantrine is cost-effective and if so, the proportion of the reduction in malaria cases and morbidity (i.e. to reduction in malaria cases and admissions) that would have to be attributed to AL required for it being cost-effective. The results of sensitivity analyses have demonstrated that even when the most conservative estimate (25% of reduction in cases attributed to

AL) of the Delphi was used, the use of artemether-lumefantrine as first line drug was found to be cost saving and to result in improved health outcomes at the same time. In conclusion, the Delphi technique has been helpful in providing a rough guide on the possible contribution of the different interventions to malaria outcomes in Kwazulu Natal. The Delphi estimates of the contribution of artemether-lumefantrine, as a first line treatment for malaria management, made it possible to undertake a cost-effectiveness analysis, albeit with limitations. Despite the questionable validity of the Delphi estimates, sensitivity analyses using the lower and upper limit Delphi estimates have made it possible to reach important policy conclusions on the cost-effectiveness of artemether-lumefantrine in Kwazulu Natal. These conclusions were confirmed by the findings in the decision tree analysis comparing SP and AL in Kwazulu Natal and in the economic analysis in Mpumalanga.

In conclusion, findings of the studies discussed in chapters 4 – 6 underscore the importance of an integrated approach to the control and management of malaria in countries where it is endemic. It has been showed that while each malaria control intervention has the potential of being cost-effective on its own (depending on various factors as previously discussed), the synergistic impact of 2 or 3 concurrent interventions results in better health outcomes and are more cost-effective together. The discussions in earlier chapters also show that malaria control will result in even better health outcomes, in terms of reduction of malaria transmission, when regional efforts of malaria control are undertaken. For example, in the Kwazulu Natal case study, the marked decline in malaria cases, admissions and deaths (discussed earlier) was partly a result of the malaria control effort (specifically indoor residual spraying) in southern Mozambique, which was undertaken as part of a regional malaria control programme under the Lubombo Spatial Development Initiative. Such efforts show that it is more beneficial to control malaria regionally since there is always movement of people between countries (hence increasing cases of imported malaria). These findings underscore the importance of both integrated malaria control initiatives as well as regional approaches to malaria control.

7.3: THE EFFECT OF ARTEMISININ-BASED COMBINATIONS ON ANTIMALARIAL RESISTANCE

Perceived overall cost of acquiring ACTs remains a hindrance to wide-scale deployment of ACTs [198]. Although ACTs are relatively highly priced compared to traditional antimalarials (that they are replacing), it is possible that the use of ACTs (which are very effective) could reduce treatment costs through reduced numbers of treatment failures and fewer malaria cases progressing to severe disease (thus needing hospitalisation), as has been found to be the case in Kwazulu Natal and Mpumalanga. The relevance of these findings in other African countries remains to be evaluated through important early large-scale implementation studies, including those in Tanzania and southern Africa [203]. There are a number of factors which may influence the relevance of the economic evaluation results to other African countries, most notably:

- the therapeutic efficacy of current first line therapy in terms of cure rates and gametocyte carriage rates,
- the intensity of malaria transmission (which is influenced by climatic and entomological factors, and by coverage with vector control interventions, mainly indoor residual insecticide spraying and insecticide treated nets),
- prevalence of treatment seeking in the informal and private sectors, and
- use of definitive diagnosis for malaria before treatment is initiated.

The short-term benefits of implementing ACT are likely to be greatest in areas where there are high levels of treatment failure of the current malaria treatment. A few studies in African countries have been published reporting levels of monotherapy treatment failure similar to those observed in Kwazulu Natal [202, 204]. However, there is concern that other countries carrying similar burdens underestimate resistance as they do not detect failures more than 14 days after treatment, even though these make up the majority of late treatment failures, as this is the follow period recommended by the WHO for countries with intense malaria transmission [205].

As ACT also decreases transmission directly by decreasing gametocyte carriage, the effect of ACT on malaria morbidity in contexts where current monotherapy is effective, such as Mpumalanga, needs to be established for areas with moderate to high intensity transmission. Although these areas with a high intensity of malaria transmission would benefit from the improved clinical cure rate associated

with ACT, the effect of intensity of transmission on the extent to which ACT will delay resistance and decrease malaria transmission is not yet resolved. In these areas with a very high intensity of malaria transmission, the effect of ACT in reducing malaria transmission may be less marked. Coverage with ACT is expected to be lower in areas of high intensity malaria transmission as a result of acquired malaria immunity (premunition), when a large proportion of parasitaemic individuals will be asymptomatic and are thus unlikely to seek malaria treatment. Furthermore even a significant reduction in Entomological Inoculation Rate (EIR) from > 100 to between 10 and 30 would not necessarily result in a decrease in the incidence of malaria.

The effect of ACT on delaying the emergence and spread of antimalarial resistance has not yet been established in Africa, although it has been demonstrated in northwest Thailand [24]. Prolonged follow up is required to evaluate the effects of ACT on resistance in southern Africa, and such studies are underway. The expectation that ACTs will delay resistance is biologically plausible [205], and established in many other diseases such as HIV/AIDS, tuberculosis and cancer chemotherapy. However, to date this has only been documented for ACT on the western border of Thailand, an area of low intensity malaria transmission (EIR < 1) [24]. In this setting most of the population is non immune and likely to become symptomatic and thus will seek treatment for malaria. Further, the Thai study site has a limited private sector and drugs are strictly regulated there, hence limiting access to monotherapy. If it is confirmed that ACTs delay the onset of drug resistance in other areas, this would provide further justification for the widespread use of ACT and would substantially increase the cost savings reported here.

The Kwazulu Natal and Mpumalanga experiences in changing treatment policy have shown that the availability of local evidence of treatment response (both in terms of cure rates and gametocyte carriage rates) is a pivotal prerequisite in motivating policy change. The information on treatment failure rates, when supplemented by evidence of changes in malaria prevalence, incidence, hospital admissions and case fatality rates becomes highly influential in guiding policy decision. In both study sites, this evidence of the potential negative consequences of not changing treatment policy was one of the most important guiding factors for senior politicians and health officials in making a decision to change treatment policy, and it appears to have weighed more heavily than acquisition cost particularly by those who appreciate the complex economic impact of malaria.

7.4: ROLE OF RAPID DIAGNOSTIC TESTS IN IMPROVED CASE MANAGEMENT AND COST-EFFECTIVENESS OF DRUGS

The extent of potential cost savings reported for Kwazulu Natal and Mpumalanga is partly influenced by the use of a definitive (rather than clinical) diagnosis for malaria, which undoubtedly contributed to minimising expenditure on ACTs. Clinical diagnosis (particularly in countries with low to moderate malaria risk) is likely to increase overall expenditure on antimalarials when ACT is implemented as first line treatment.

Confirmed diagnosis of malaria is a corner-stone of any strategy of case management. A critical aspect of whether or not ACTs would be cost-effective in different settings is related to the techniques used for diagnosing malaria in those settings. Clinical diagnosis, widespread in most of Africa and encouraged by the World Health Organisation (WHO) recommendation that prompt access to antimalarial treatment should be given to all patients with fever in areas or seasons of high transmission, has resulted in unnecessary and inappropriate overuse of antimalarials and the resultant increased drug pressure and consequently drug resistance. The WHO recommendation largely relied on inexpensive drugs (chloroquine and sulphadoxine-pyrimethamine) and on the relatively higher cost of rapid diagnostic tests or malaria smears. However effectiveness of these drugs has been eroded by the spread of resistance in most parts of the world [2].

There is now a strong justification to argue the case for routine use of definitive diagnosis as the basis for treatment with ACTs as a part of a comprehensive package for malaria control and as an integral part of case management in particular. Findings discussed in chapters 4 and 5 have shown that the routine use of definitive diagnosis as part of case management has been instrumental in promoting efficient use of antimalarials, and findings discussed in chapter 6 have demonstrated that the use of definitive diagnosis as part of case management plays a critical role in determining whether on not new antimalarials are cost-effective, when compared to treatment based on clinical diagnosis. The accuracy of the performance of an RDT should be underscored. The World Health Organisation recommends that RDTs should have a sensitivity of close to 95% and be highly stable (i.e. have a long shelf-life) and provides guidelines on the operational requirements for RDT use [197]. Indeed, the case for routine use of definitive diagnosis is justified on the following grounds:

- ★ Firstly, as malaria control improves as a consequence of widespread use of insecticide treated bed nets, indoor residual spraying and/or ACT use [24], the number of suspected malaria (fever) cases which would be definitively diagnosed as malaria will decrease. Consequently the introduction of definitive diagnosis with RDTs prior to or at the same time as the introduction of ACT would become increasingly cost saving, because there would be fewer suspected cases to test and considerably fewer cases to treat.
- ★ Secondly, with newer and more expensive drugs now being considered or used for first line treatment, methods of ensuring more efficient use of drugs need to be considered [7]. Restricting the use of antimalarials to only those definitively confirmed to have malaria parasites, even in areas of moderate to high intensity malaria transmission could be one way of reducing antimalarial costs and ensuring more rational use of these drugs [27].
- ★ Thirdly, the optimal use of antimalarials (particularly the ACTs) is increasingly becoming more critical in the face of possible inadequate supply of ACTs in the quantities required which is becoming imminent as more countries start using them for first line treatment [187].
- ★ Lastly, limiting antimalarial use through RDTs should decrease the drug pressure which selects for antimalarial use. If this is confirmed, the long term cost effectiveness of RDTs could be substantially increased.

Evaluation of the costs and benefits associated with the introduction of definitive diagnosis, and whether this would be affordable, in resource-poor countries is of paramount importance before wide-scale implementation. The effectiveness of RDTs as a diagnostic tool has been assessed in various settings and some of the products have been found to have a diagnostic sensitivity as high as that of microscopy [6, 8]. There seems to be consensus in the literature that RDTs are the most practical alternative for definitive diagnosis in resource-poor settings where microscopy is not available or feasible [6, 61, 86]. However, the cost and affordability of RDTs remains the centre of the debate as to whether antimalarial treatment should be provided on the basis of clinical or definitive diagnosis. While several authors have alluded to the cost and cost-effectiveness of RDTs [2, 7, 58], very few studies have documented both the economic costs and benefits of using RDTs. Goodman and others estimated the costs and cost-effectiveness of dipsticks in different settings [27], while Pang and

Piovesan-Alves use the cost-minimisation approach to compare the costs of dipsticks to the cost of microscopy [195].This study has attempted to document the costs and benefits of using RDTs, using data on the numbers and age distribution of cases with clinically suspected malaria, presenting to public sector health care facilities in southern Mozambique (chapter 6). A range of probabilities of malaria being confirmed has been explored as this is expected to decrease rapidly with the introduction of an effective IRS programme, and further with the implementation of an ACT policy.

Findings presented in chapter 6 show that considerable savings on costs of managing malaria patients are achievable with the introduction of definitive diagnosis (using RDTs). Findings also demonstrated that cost-saving are achievable even when a narrow perspective focusing only on costs of the RDTs and costs of antimalarials. It should, however, be noted that a wider perspective of malaria-related treatment costs (i.e. to include 'other costs' of facility-based malaria case management services) – as shown in Figure 6.4 – reveals that introducing definitive diagnosis results in even higher costs savings. Some may argue that these "other costs" should not be taken into account as patients testing negative for malaria would still need to be treated and that these costs would therefore still be incurred by the public sector provider. However, it could equally be argued that a fair proportion of those who are incorrectly treated for malaria on the basis of clinical diagnosis alone will return to the facility for re-treatment for an illness other than malaria when antimalarial treatment fails and that it is thus appropriate to include these "other costs" in the evaluation. Patients returning with treatment failure would increase patient load at a health facility, hence increasing the burden on staff time and use of other resources. The consequences of misdiagnosis go beyond increasing the patient load at health facilities to increasing drug pressure selecting for drug resistance which leads to a range of medical, social and economic consequences. Amexo and others illustrate that there are consequences at individual, household and national levels. Among others, the consequences include prolonged and severe illness, drug side effects, loss of faith in health services, increased expenses on transport and treatment seeking, loss of household income, and inaccurate public health data and hence unreliable information for planning and budgeting [7]. It has also been argued that the effects of malaria misdiagnosis fall most heavily on the poor and vulnerable who are least able to withstand prolonged ill-health and the associated missed opportunities for earning income [7]. If all these are quantified into monetary terms, the use of definitive diagnosis (with RDTs) is likely to be more cost saving and or cost-effective.

Furthermore, findings presented in chapter 6 suggest that restricting the use of RDTs to patients over 6 years of age yields higher cost savings than the use of RDTs in all febrile cases – particularly in areas of higher intensity malaria transmission. Thus, while the use of RDTs in all suspected cases has been shown to be cost-saving in some instances, targeting RDTs at the group older than 6 years and treating children of 6 years or less on the basis of clinical diagnosis is even more cost-saving (see Figure 6.2). This is largely due to the fact that nearly three-quarters (71.7%) of those presenting with possible malaria in the Mozambican facilities studied were either school-going children or adults (i.e. the group whose malaria treatment course costs substantively more than the treatment course of children 6 years or younger). The finding that use of RDTs in patients older than 6 years is more cost-effective is not surprising given that the current cost of the RDT ($ 0.95) is higher than that of AS+SP treatment in a child aged 1-6 years ($0.49), and is similar to the cost of artemether-lumefantrine for this age group ($0.90). The justification for the restriction of use of RDTs in patients older than 6 years becomes more appealing when one considers the fact that in high transmission areas children under 5-years carry the largest malaria disease burden (as they have not yet acquired immunity) and that many health care providers would find it problematic to deny antimalarials to those who test negative in this group.

The malaria prevalence level at which introducing definitive diagnosis with ACT becomes cost effective needs to be considered for each country or study site, as there is marked variation in malaria prevalence and age distribution of both clinically suspected and confirmed malaria. Age distribution is important because the costs of rapid tests remain constant across all ages, while the costs of ACT increase with age.

The findings on the cost-effectiveness of using RDTs were found to be sensitive to the effects of changes in *age distribution* and prevalence of malaria parasites in patients with clinically suspected malaria, and *price of ACTs* and *price of RDTs*. Results show that increasing proportions of older febrile cases result in increased cost savings with RDT introduction. That is, the higher the proportion of adults in the group presenting with malaria symptoms before testing, the higher the costs savings associated with testing all febrile cases and treating those confirmed to have malaria. As explained

above, this finding is reasonable because the price of RDTs is fixed across all ages while the price of antimalarials is dependent on age categories (where the adult treatment course is always more expensive than the treatment course for children). Results also showed that as the prices of ACT increase, RDT implementation becomes increasingly cost saving. However, when less expensive ACTs (e.g. AS+SP) are introduced, the price to the health care provider should be $0.65 or lower for RDTs to be clearly cost saving in populations with over 52% of clinically diagnosed malaria cases being confirmed malaria cases (quadrant 2, Figure 6.8). As expected, the results showed that the use of RDTs will become increasingly cost-effective as the price of RDTs reduces.

While the results of this study suggest that the introduction of RDTs could be beneficial as an integral part of malaria case management (particularly with the use of ACTs), there are a number of potential difficulties associated with RDTs that should be considered and addressed by policy makers before wide-scale implementation of routine use of RDTs.

- ★ Although a range of malaria RDTs have performed with high accuracy in both laboratory and field based studies [186, 206, 207], several studies report RDT sensitivities and specificities below 95% [85]. Of additional concern is the lot variability reported and the potential of RDTs to denature with exposure to high temperature and humidity. Thus, effective use of RDTs would require strict quality assurance and adequate transportation and storage arrangements must be made.

- ★ The benefits of RDTs would not be realised if the health workers prescribe antimalarials without taking into consideration the results of the test. The World Health Organisation recommends that treatment algorithms should allow antimalarial treatment of severe (but not uncomplicated) malaria cases in which the RDT result is negative. Appropriate further investigation of all fever cases with negative RDT result is essential. Thus, the diagnostic assessment should be comprehensive enough to include both the RDT result as well as clinical assessment.

- ★ For treatment of fever cases testing negative for malaria, some formal or informal health care providers may still use antimalarials and there is an increased risk of irrational use of other drugs, particularly antibiotics. This necessitates integrated training of health workers in

rational drug use for the treatment of non-malaria fever cases and enhanced drug utilisation monitoring, particularly at the time of RDT introduction. Village health volunteers in Laos were found to only require minimal training (1 hour) to sustain reliable use of RDTs over a 10 month period [207].

- ★ Lastly, in most malaria endemic countries, access to preventive, diagnostic and curative services remains limited due a range of constraints, particularly cost (of treatment seeking, diagnosis, drugs and of transport). Care should be taken to ensure that the costs of new and apparently cost-saving interventions, such as RDTs, are not borne by households.

The broader relevance of the findings on the cost-effectiveness of routine use of RDTs (that is to other settings) is highly dependent on contextual issues (age distribution among the febrile cases, type, price and quality of RDTs and ACTs), as well as the characteristics of the health systems in place (including health care seeking and provider behaviour and practices, access to malaria diagnostic and treatment services). Further, the interpretation of the findings presented and discussed in chapter 6 needs to be done cautiously taking into consideration the methods used for undertaking the cost-effectiveness analysis, should particularly note the following:

- ★ Although the additional (indirect) benefits of limiting the use of ACTs to patients in whom the malaria diagnosis is confirmed could not be included in this study, these are considered likely to be substantial. Excluding malaria would facilitate earlier diagnosis and treatment of the actual cause of the disease for those who are malaria negative, and would minimise the treatment seeking costs related with repeat visits and the productivity losses associated with prolonged illness. In addition, the use of definitive diagnosis would provide more reliable data on malaria cases, hence allowing for accurate forecasting quantities of antimalarials required, planning and budgeting. Also, drug pressure, and consequently, the rate of spread of antimalarial resistance could be decreased. Lastly, restricting the use of ACTs to those who can benefit could contribute to preventing problems caused by the current global shortage of ACTs manufactured according to Good Manufacturing Practice (GMP) requirements [208].

- ★ Further, the analysis of the potential benefits of introducing RDTs in combination with ACTs is more complex if the majority of malaria treatment is self-administered or sought in the private

and informal sectors. In the two districts studied (southern Mozambique), which are largely rural, people mainly seek care for malaria treatment from public health facilities. This being the case, the study did not address the scenario where the majority of patients seek care in the private or informal sector and/or self-administer treatment. In areas where this is the case, WHO recommends that "*it is appropriate that malaria RDTs are used in this sector under similar conditions to those recommended for public services*" [62, pp. 10].

- As this study was conducted within a pilot evaluation of RDT and ACT introduction at district level with health care provider training and supervision in RDT use being integrated with that of case and drug management, the costs of policy change, training and supervision for the implementation of the RDTs, could not be determined. Cost of implementation will vary in different settings, depending on the approach used for the introducing RDT as part of routine malaria screening, the approach used for training health workers, the type and quality of RDTs use, and the transport, storage and quality assurance systems put in place. These costs are likely to be to be high in settings where the health system infrastructure is rudimentary.

7.5: THE RELEVANCE OF THIS STUDY'S FINDINGS TO OTHER MALARIA ENDEMIC COUNTRIES

The experiences of Kwazulu Natal and Mpumalanga are not sufficient to estimate the cost of policy change (including the implementation of the new treatment policy) in other settings, as provincial costs in South Africa are likely to be considerably lower than in other countries where the scale of the malaria burden is much larger, where malaria control, surveillance and monitoring activities are not well established, and where regular meetings of malaria policy makers and training of health workers are not routine. Obviously, the process and implementation costs would have been substantially higher if new staff had to be employed to formulate and implement such a policy change, in the absence of institutions routinely responsible for such activities. Where there is a relative lack of existing malaria control capacity, this may also translate into a lower effectiveness of policy change given the time required for developing new capacity. In settings where higher implementation costs are incurred, cost savings documented in the cases of Kwazulu Natal and Mpumalanga are likely to be somewhat eroded, but ACTs could still remain cost-effective.

Furthermore, Kwazulu Natal and Mpumalanga were found to have a relatively reliable, well regulated drug supply, which is expected to be an important factor for deriving the greatest benefit from implementing ACT. The high coverage of ACT treatment that was achieved by implementing AL and AS+SP in the public sector alone in Kwazulu Natal and Mpumalanga, respectively, resulted from the community's preference for seeking treatment in public sector facilities. Household surveys conducted in Kwazulu Natal and Mpumalanga in 2001 revealed that 99% of the respondents opted to seek care from a public facility when they had malaria. The implementation of ACT in other malaria endemic settings (particularly in Africa) requires careful planning and adequate resources to ensure reliable ACT availability to optimise coverage and thereby maximise the benefits of ACT. Although similar treatment seeking behaviour was reported in southern Mozambique and Kwazulu Natal (S. Dlamini, Social Scientist, Medical Research Council, *Personal Communication*), the extent to which this could be scaled up to national level in Mozambique or applied to other countries would depend on understanding treatment seeking behaviour in a given setting and also on whether there is reliable ACT supply to all major sources of health care.

In summary, the broad relevance and generalisation of these findings to other malaria endemic countries is dependent on various factors including whether or not:

- The intensity of malaria transmission which is determined by climatic and entomological factors and by the use of vector control measures as discussed in Section 7.2 above. The intensity of malaria transmission influences the level of coverage and adherence with ACTs that is achievable.

- Adequate health systems in the health sector are in place. If these are in place, they determine the extent to which change of treatment policy will be easily implemented and effected. The quality of health services in the public sector has a bearing on whether patients will seek care in the public sector or not. Inadequate public sector health services are likely to result in increased treatment seeking in the private sector (both formal and informal). Heavy reliance on the private sector for treatment of malaria, particularly if it is not well regulated, may not yield the same results on cost-effectiveness of ACTs.

- Equally important is the need to have health services provided free of charge in public health

facilities. If it is not feasible to provide health care free for all services, at least governments should ensure that their populations can access free services for malaria treatment. It has already been noted that the burden of malaria is heaviest for the poor and that the poor are more at risk because they are less likely to have the means to employ preventive measures against malaria (such as use of bed nets). In view of this, services for the management of malaria should be made accessible to the poor by making them free of charge at all public health facilities. Availability of free health services will also be helpful in reducing seeking care from the informal providers of care (e.g. vendors and shopkeepers) who charge less than public clinics.

- Related to the issue of health systems (in terms of providing care) is the critical issue of regulation on the use of antimalarials (including the use of either of the components in an ACT as monotherapy) in the informal sectors and that of ensuring that the quality of antimalarials on the market (in both formal and informal private sector).

- Implementation costs (especially on a wide scale) for the change in first line treatment policy are very high. High implementation costs are likely to erode the cost-savings associated with the use of ACTs. While ACTs could still remain cost-effective even when costs of change of treatment policy are high, they would not be as cost-effective (or cost-saving) as when the implementation costs are relatively low.

- There is high coverage with the use of ACTs in relation to the proportion of people who need antimalarial treatment. The higher the coverage the more effective the ACTs will be in reducing malaria transmission and therefore the better the health outcomes associated with their use. From the studies discussed in chapters 4 and 5, there was very high coverage (95%) with the use of ACTs, mainly due to the fact that there was high treatment seeking (98%) for malaria care in the public sector. This means that the vast majority of people needing treatment for malaria actually received the correct antimalarial. High coverage is also enhanced by the extent to which there is sufficient regulation of other antimalarials (especially of monotherapy drugs) on the market. In the study sites considered, due to their rural nature, it was difficult to obtain other antimalarials from other sources. In fact, even within the public health system, all other monotherapy antimalarials were removed so that health care providers could not continue to dispense them to patients.

- ★ Related to the above issues is that of patient adherence to the completion of a treatment course of antimalarials. Lack of adherence to treatment is likely to result in treatment failures and to bring the onset of resistance to the antimalarial in question. Although adherence to treatment is a relatively difficult phenomenon to measure, ensuring that factors that would improve adherence is of critical importance. Such factors include: (if possible) use of an antimalarial whose dosage schedules are not complicated; adequate patient education on how to take the medicine by qualified health personnel; making the antimalarials freely available at the point of seeking care; and improving access to health services in general (in terms of distance, quality of health services, and free or minimal costs of seeking care).

- ★ Routine diagnosis of malaria relies on definitive or clinical diagnosis. As noted previously, reliance on clinical diagnosis results in over-diagnosis of malaria and unnecessary use of antimalarials. Findings presented in chapter 6 have shown that cost-savings associated with the use of definitive diagnosis is partly due to reduced misuse of antimalarials. This is particularly true in the case of ACTs which are considerably highly priced.

8. CONCLUSIONS & RECOMMENDATIONS

8.1: CONCLUSIONS

Cost-effectiveness and affordability of ACTs is one of the issues for major debate around the replacement of traditional cheaper antimalarials with ACTs as first line treatment for uncomplicated malaria. Early results on the impact of malaria control policy changes in Kwazulu Natal and Mpumalanga suggest a synergy between effective vector control and widespread and rational use of Artemisinin-based combination therapy (ACT).

Following improved IRS and the change of malaria first line treatment policy in Kwazulu Natal, there was a massive reduction in malaria outpatient cases which resulted in efficiency gains. The regional effort of indoor residual spraying in southern Mozambique positively enhanced the synergies of the malaria control interventions in Kwazulu Natal. This study found that in the absence of such massive declines in the number of malaria outpatient cases, health facilities would have been over-burdened with potentially unbearably higher workloads for health workers (given the AIDS epidemic in Kwazulu Natal), and probably reduced quality of care.

This study's objectives have been met. This study has documented the impact, in terms of health outcomes, associated with the use of ACTs as first line treatment in Kwazulu Natal and Mpumalanga; the cost savings (or additional costs) resulting from the change of treatment policy from monotherapy to ACTs in Kwazulu Natal and Mpumalanga; the cost-effectiveness of two ACTs (AL and AS+SP) relative to SP; the costs associated with the use of Rapid Diagnostic Tests (RDTs) to explore the role of introducing definitive diagnosis together with the change to ACTs; and has explored the use of economic models and Delphi surveys as a way of dealing with methodological challenges in economic evaluations. Lastly, the recommendations on the cost-effectiveness of ACTs and RDTs, in southern African settings with effective vector control programmes are provided.

Results of the economic evaluation studies in Kwazulu Natal and Mpumalanga have demonstrated that the change in treatment policy from SP monotherapy to AL or AS+SP resulted in both improved health outcomes as well as reduced costs. From these two studies, it can be concluded that ACTs can be both cost-saving and cost-effective in settings that are similar to Kwazulu Natal and Mpumalanga (such as, the northern border of Thailand). Cost savings associated with the implementation of artemether-lumefantrine (AL) and artesunate+SP (AS+SP), in Kwazulu Natal and Mpumalanga respectively, result from the improved clinical cure rates and decrease in malaria transmission. The use of ACTs for first line treatment could potentially result in greater cost-savings, than those reported in chapters 4 and 5, if costs and health outcomes for the entire province are considered. The extent to which similar results can be achieved in other settings requires detailed consideration.

An important issue that has not been explored in this study is the assumption that the delivery of ACT through private formal and informal outlets is always undesirable. Although more studies need to be undertaken in different context to ascertain the desirability of delivering ACTs through informal providers. D'Allessandro and others, in their study on whether ACTs should be used in home-based management of fever strategy in Uganda, conclude that "...the use of ACTs in HMM approach should be carefully reconsidered because the potential benefits might be outweighed by the negative consequences" [200, p.1]. They continue to argue that this does not mean that ACTs can never be deployed in home-based management of fever, but careful consideration of the pros and cons should precede their deployment (*ibid*). The possible deployment of ACTs in the private (formal and informal) sectors is particularly important in settings where utilisation of public health facilities is low (as is sometimes the case in some African countries). In such settings, having ACTs available in the private sector would improve on ACT coverage, which is a key factor in ensuring proper management of malaria as discussed previously.

Findings of this study confirm that ACTs can be cost saving and cost-effective, even in the short term, in the context of low transmission of malaria. This study found that short term cost-effectiveness of ACTs is highly dependent on other contextual issues, including:

- the concurrent malaria control interventions (particularly IRS),

- ★ the restriction of ACTs to patients who have been confirmed as having malaria using definitive diagnosis,

This study has not specifically assessed the role of other contextual factors, but other factors that are likely to have contributed to the cost-effectiveness of ACTs include:

- ★ high coverage with the use of ACTs (i.e. proportion of the population who need antimalarials who actually get ACTs),
- ★ the level of development of health infrastructure and its capacity to implement and monitor use of ACTs and to ensure minimised use of monotherapy drugs,
- ★ the price of ACTs as well as the price of the diagnostic tests and the antimalarial being replaced by ACTs, and
- ★ patients' compliance to treatment regimens.

Similar conclusions have been reached by several authors [15, 68, 152] who have demonstrated the cost-effectiveness of ACT in the medium- and long-term. The focus on the longer term is based on the need for finding antimalarials that delay the emergence and spread of resistance, while continuing to provide effective treatment. This should be the priority of any country facing the problem of resistance to antimalarials.

From this study, AS+SP has been found to be more cost-effective than artemether-lumefantrine in the short term. This is expected because AS+SP is cheaper than artemether-lumefantrine, while both had cure rates of 99% in their respective study sites. It is important to note, however, that AS+SP can only be used in places where resistance to SP monotherapy is low (as was the case in Mpumalanga), otherwise its effectiveness in reducing number of malaria cases and admissions would be reduced. As lumefantrine has never been used in Africa as monotherapy, its "useful therapeutic life" is expected to be longer than that of artesunate plus SP (or plus amodiaquine). In areas with established SP (or AQ) resistance, artemether-lumefantrine, despite being more expensive than AS+SP, might turn out to be more cost-effective.

The use of early detection of malaria and treatment with ACT – in line with the WHO strategy of 'early diagnosis and effective treatment' – has been shown to reduce morbidity and mortality, and at the same time slow the progression of resistance [198]. With improvements in vector control (through indoor residual spraying or insecticide-treated nets) and higher costs of antimalarial treatment, there is increased opportunity for saving costs through the introduction of rapid diagnostic tests in facilities where microscopic confirmation of malaria diagnosis is not reliably available. As noted by Amexo and others, it is unethical to continue with high levels of malaria misdiagnosis in light of the introduction of expensive antimalarials and availability of cost-effective methods of diagnosing malaria (e.g. use of RDTs) [7]. Provided that rapid diagnostic tests with high sensitivity and specificity (of > 95%) are available at below $0.65 per test, this intervention would be cost saving for populations with a similar age distribution to those studied in southern Mozambique, provided fewer than 52% of clinically diagnosed malaria cases require antimalarial treatment (AS+SP). Cost savings are greater if the ACT in use is more expensive (e.g. artemether-lumefantrine) or if the symptomatic population has an older age distribution or if the price of RDTs is lower than the current cost of $0.95 per test. In conclusion, rapid, accurate and accessible detection of malaria parasites has an important role in addressing the problem of malaria misdiagnosis and inappropriate use of antimalarial drugs. In the context of low to moderate intensity malaria transmission and treatment with expensive antimalarial drugs, RDTs have been found to be cost-saving and cost-effective within the constraints of price of RDTs, price of antimalarial being used for treatment and the age distribution of malaria patients. In this era where the use of ACTs is being globally encouraged and even financed, strategies such as the concurrent use of ACTs and RDTs should be equally encouraged and financially supported.

Results of this study have demonstrated the importance of including "other recurrent and capital cost" in the analysis. Although policy makers normally consider only the acquisition cost of antimalarials and/or diagnostic tests, when making policy decisions about change of malaria treatment policies, it is important to consider all costs that are involved in providing a service. Exclusion of "other costs" (which can sometimes make up more than 60% of the total costs of providing a service) provides an incomplete picture on costs of managing malaria patients. Most certainly, from an economic point of view, services for malaria management cannot be provided without health workers or a health facility.

Despite the methodological challenges associated with the cost-effectiveness analysis of ACTs, particularly in the context where confounding factors make it rather cumbersome to quantify actual impact of the ACT intervention, techniques such as Delphi surveys have proved helpful in addressing these methodological challenges.

8.2: PHD CONTRIBUTION

The overall goal of the studies discussed in this thesis was to evaluate the cost-effectiveness of artemisinin-based combinations, in light of the recent advocacy for their use as first line treatment of uncomplicated malaria in endemic areas, particularly in Africa where the burden of disease is the highest and where severe financial constraints acutely threaten sustainable acquisition of these drugs for all those who need them. Although ACTs have recently become widely recommended, and their effectiveness has been well established, there are very limited studies that have comprehensively evaluated them to explore their cost-effectiveness (and safety) over a prolonged period of time. The SEACAT evaluation is one such large long-term study that has set out to comprehensively evaluate ACTs in the South-East African setting.

The work presented in this thesis is based on my work on the SEACAT evaluation, which comprised 8 components. I was the principal investigator of the economic evaluation component of the SEACAT evaluation. The work that I undertook on the SEACAT project is a lot more extensive than what has been presented in this thesis. Specifically, my tasks as the principal investigator included designing the CEA studies in the different countries and study sites; developing tools for data collection, collecting baseline and post-intervention data from 6 study sites (in 3 countries); analysing these data for various purposes and audiences (e.g. presentations at international conferences, specialised meetings, dissemination to key stakeholders, etc). In addition, I was responsible for writing various project reports. While these activities were being undertaken as part of the SEACAT project, it was clear from the outset that some of the data would be used for the PhD thesis. The scope of the thesis was developed by me and in deciding this I was largely guided by the type of data expected to come from the project and timeframes involved in obtaining relevant data for the thesis. For example, considering that some of the study sites (e.g. Limpopo in South Africa, as well as the study sites in Mozambique and Swaziland) were taking long in making the decision to implement ACTs, it became

clear that post-intervention data from these sites would only be available many years later. For this reason, the thesis was restricted to assessing the cost-effectiveness of ACTs in only 2 study sites, where all data required would be available within a reasonable timeframe. Among others, the assignments that partly feed into the findings presented in this thesis include:

- ★ Designing the household survey questionnaire that was translated into several local languages and used in all the SECAT study sites (in 3 countries).

- ★ Training research assistants and supervision of data collectors for the household survey in Kwazulu Natal and Mpumalanga, as well as analysing the survey results and writing a number of project reports with the household survey results.

- ★ Presenting results on the costs, effectiveness and cost-effectiveness at several fora including the Multilateral Initiative on Malaria (MIM) Conference, the South African Malaria Conference, the 4th and 5th International Health Economics Association (iHEA) conferences, World Health Organisation *Rapid Diagnostic Tests* a Technical Consultative meeting[20] in Geneva and at specialised meetings/workshops in South Africa.

- ★ Some of the results presented in chapter 4 were also presented in a report commissioned by the US Institute of Medicine National Academy of Sciences Committee on the Economics of Antimalarial Therapy (who commissioned me to write a paper on the Kwazulu Natal findings). These findings fed into their important policy making process and they were used in writing a book entitled "Saving lives, buying time: economics of Malaria Drugs in an age of resistance."

- ★ Writing a publication based on the Kwazulu Natal findings. The title of the article is: "Artemisinin-based combination antimalarials save money: a case study of Kwazulu Natal in South African." *International Medicine and Tropical Health;* September 2004. Another publication has been drafted and is the process of being finalised for submission It is entitled: *"Should countries implementing an Artemisinin-based combination malaria treatment policy also introduce Rapid Diagnostic Tests?* A publication of the economic evaluation in Mpumalanga is currently being drafted.

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[20] The summary of issues arising from this meeting have been published in a WHO publication (2006): "The role of laboratory diagnosis to support of malaria disease management: focus on the use of rapid diagnostic tests in areas of high transmission." Report of a WHO Technical Consultation.

The studies findings presented and discussed in this thesis have explored the cost-effectiveness of ACTs in different contexts with low intensity malaria transmission. While most studies on cost-effectiveness of ACTs have relied on economic and epidemiological modelling using secondary data from various study sites and from clinical trial data, the findings of the studies discussed here are based on actual primary data collected from the selected study sites. The results discussed in this thesis provide real-life experiences, as far as costs and cost-effectiveness are concerned, and thus form a more valid and acceptable basis for conclusions on deployment of ACTs in contexts similar to South Africa than economic models alone. The discussion highlights the recommendations on deployment of ACTs in settings that differ from the study sites. The empirical results on the costs and cost-effectiveness of ACTs in a low transmission setting are the major contribution of this thesis. However, in undertaking some of analyses presented (especially the decision tree models) and in discussing the relevance of the findings presented in the thesis, I have drawn on some of the findings of other components of the SEACAT project. For instance, data on some of the variables of the model was either obtained from other SEACAT project components and/or secondary data. The focus of this study was the evaluation of two ACTs (AL and AS+SP), but the findings of cost-effectiveness can be generalised to other ACTs that have the same effectiveness, characteristics and prices as those studied. Additionally, this work explores methodological issues relating to conducting cost-effectiveness analyses in contexts where the typical CEA techniques are not adequate.

In addition, the work presented in this thesis explores one critical factor (i.e. the routine use of definitive diagnosis) that influences the cost-effectiveness of ACTs. The role of using definitive diagnosis (specifically RDTs) before treatment with ACTs was studied, in light of the fact that the new antimalarials (ACTs) are relatively more expensive than the traditional monotherapy antimalarials. The rationale for routine use of definitive diagnosis lies in the fact that restricting the use of ACTs to only those who need them minimises irrational use (and hence saves costs) and is likely to protect them from rapid development of resistance, thus prolonging their useful therapeutic life. Considering the fact that the South African study sites where ACTs were being evaluated already had use of definitive diagnosis in place, the evaluation of the role of rapid diagnostic tests was undertaken in two Mozambican study sites to establish their role in improving malaria case management and in the cost-

effectiveness of ACTs. In the context of using ACTs for first line treatment, the evaluation of the role of definitive diagnosis, particularly with RDTs that are usually considered to be expensive and unaffordable, is another key contribution of this thesis. Clearly, while a lot of work has been done on evaluating the performance (accuracy and stability) of RDTs, very little work has been done on assessing their costs and cost-effectiveness [197]. Information on cost-effectiveness of RDTs is particularly important in the era of wide implementation of ACTs.

The work presented in this thesis explores the use of other methodologies to augment the standard economic evaluation techniques. In particular, the need to disaggregate the impact of three interventions, in order to undertake a cost-effectiveness analysis of only one of them, required methods which were far beyond the standard economic evaluation techniques. This challenge was addressed using the Delphi survey, which was undertaken to elicit the percentage contribution of each of the interventions that were believed to have contributed to the changes in health outcomes between the baseline year and the year of evaluation. The combined use of the Delphi technique and comparison of CEA results from another study site, to explore the cost-effectiveness of artemether-lumefantrine in Kwazulu Natal, is another key contribution to the CEA methodology in a setting where the actual impact an intervention cannot be easily disaggregated from the total impact of several other interventions. In addition, as has been demonstrated in chapters 4 and 5, the use of ACTs has an impact on both costs and health outcomes associated with uncomplicated malaria (i.e. treated as outpatients), as well as those associated with severe malaria (i.e. treated as inpatients). In order to capture the overall impact of ACTs, decision tree models were used. The results of the decision tree models, for Kwazulu Natal and Mpumalanga, confirm the earlier findings and conclusions reached; that ACTs are more cost-effective than SP monotherapy. In addition, the results of the models allowed more direct comparisons to be made between AS+SP and artemether-lumefantrine.

A comparative analysis of the cost-effectiveness of two ACTs in similar settings, has not only provided insight into the factors that influence the cost-effectiveness of ACTs, but has also allowed the exploration of the reliability of the Delphi estimates used in Kwazulu Natal. Lastly, this is the first study that has explored the cost-effectiveness of ACTs and of using rapid malaria diagnostic tests as the basis for ACT treatment, in the context of effective vector control at local and regional levels.

8.3: RECOMMENDATIONS

Based on the findings of the studies presented in this thesis and other experiences documented in peer-reviewed articles [3, 15, 27, 59, 62, 68, 73-75, 89, 177, 181, 183, 196, 197, 209, 210], the following recommendations are suggested:

1. Based on the findings of the SEACAT project, the results from study sites in South Africa and Mozambique have demonstrated that an integrated approach to malaria control and management results in optimised malaria health outcomes, in view of the global goals to dramatically reduce malaria morbidity and mortality (i.e. with reference to the Millennium Development goals and the Arusha goals). Reliance on one strategy alone (either IRS or use of ITNs, or improved case management, among others) does not result in maximum potential health outcomes. The results from the SEACAT study sites (in Kwazulu Natal, Mpumalanga and Mozambique) presented in this thesis have demonstrated that such an integrated approach is critical in rolling back malaria. On the basis of the findings from the SEACAT project and the results presented in this thesis on cost-effectiveness of interventions, it is recommended that countries with a heavy malaria burden should seek to implement integrated strategies, as opposed to single strategies. The higher the effectiveness and coverage of these interventions, the better the health outcomes.

2. With increasing globalisation and regional initiatives at various levels, governments should consider joint efforts at regional level for controlling malaria. The implementation of interventions at regional level, such as IRS, yields better outcomes in terms of malaria transmission, as demonstrated by the highly successful Lebombo Spatial Development Initiative in Kwazulu Natal and southern Mozambique. On the basis of the key lessons learnt from the SEACAT project, one can recommend that neighbouring countries should consider dialogue on regional strengthening of malaria control, and should aim to use antimalarials in such a way that the whole region benefits. For example, it makes sense for countries in the same region to dialogue at a time when a change in first line treatment policy is being considered and debated. Hopefully, through such dialogue, countries would be able to benefit from choosing similar policies for the management of malaria.

3. The high levels of ACT coverage (>90%) achieved by introducing ACTs in the South African public sector only was a key driver of the marked impact on malaria cases. Countries should endeavour to educate their populations on malaria case management options and the services available at the public health facilities. The services for the treatment of malaria should be provided **free of charge** to all people, and the populations should be encouraged to seek care at public health facilities. Self-treatment and seeking care from the informal sector and traditional healers should be discouraged. This requires comprehensive and extensive information, education and communication (IEC) on malaria-related matters – including treatment seeking in the public sector, adherence with the full treatment course and acceptance of vector control measures. Furthermore, reliable supply of quality ACTs and regulatory systems that discourage the use of monotherapy and ensure compliance to treatment guidelines are needed.

4. ACTs were both cost effective and cost saving in Mpumalanga, where SP monotherapy had high cure rates and effective vector control had led to low intensity malaria transmission. Based on the findings presented in this thesis, it is recommended that countries with low intensity of malaria transmission, and with contextual settings similar to South Africa, should consider switching to ACTs regardless of the level of effectiveness (cure rate) of the existing policy if the current policy is associated with high levels of gametocyte carriage (as is often the case with SP monotherapy).

5. One of the findings presented in the thesis is that relatively more expensive ACTs (e.g. artemether-lumefantrine) are likely to be less cost-effective than the relatively cheaper ones (such as AS+SP). On the basis of this finding, it is recommended that countries facing severe budget constraints could switch to relatively less expensive ACTs such as artesunate+SP or artesunate+amodiaquine, provided adequate cure rates are achieved by these combinations.

6. On the basis of the findings presented in chapter 6 of the thesis, it is recommended that in areas of low to moderate intensity malaria transmission, particularly where the adults make up a bigger proportion of people presenting with malaria, routine use of definitive diagnosis (and more specifically RDTs in areas where microscopy is not available) before treatment should be the basis for treatment with an ACT. Further, it is recommended, based on the findings of this thesis, that in situations of inadequate resources for purchasing RDTs, the use of RDTs for routine testing for malaria can be restricted to patients older than 6 years. Even at a price of $0.95 per test, it will be beneficial to introduce routine use of RDTs before treatment, if ACTs are being used for treating malaria in areas of low to moderate intensity transmission. However, countries are encouraged to negotiate a price of $0.65 or lower per test if they want to maximise gain from using RDTs.

7. The use of the Delphi technique and economic models discussed in this thesis has demonstrated that cost-effectiveness analysis can still be conducted even in circumstances of challenging methodological gaps. In this study, the use of the Delphi technique has proved useful in disaggregating the effect of 3 malaria control interventions to allow for the evaluation of only one of the interventions (in the Kwazulu Natal study site). Further, the use of decision tree models proved useful in synthesizing the multifaceted impact of ACTs (i.e. at outpatient and inpatient levels), and other interventions (in the case of Kwazulu Natal). Researchers are encouraged to use such techniques to overcome methodological hurdles.

8. Lessons learnt from the SEACAT project show that once countries have switched to ACTs, they should strive to ensure that there is over 90% coverage (i.e. have a very high proportion of people needing malaria getting the correct drug in the correct dosage), and they should try as much as possible to put in place regulatory systems that discourage the use of ACTs in informal settings (e.g. having ACTs sold by street vendors and/or shopkeepers). It is recommended that ACT should be co-formulated or at least co-packaged to improve compliance and minimise the use of monotherapy.

8.4: KEY AREAS FOR FURTHER RESEARCH

As the studies presented in this thesis have evaluated the cost-effectiveness of ACTs in specific contexts, the conclusions reached need to be interpreted with caution in different contextual settings. The specific contextual issues of the study settings and the broader relevance of the findings have been discussed. The assumptions and limitations of the studies presented in the thesis have also been highlighted. In order to have a better understanding of the cost-effectiveness of ACTs in different settings, the following research areas need to be addressed:

- ★ While it would be desirable to conduct comprehensive economic evaluations of ACTs in settings where there are no confounding factors to the impact of ACTs on malaria transmission and on improvement of health outcomes, it is often not feasible and may not be ethical, to evaluate wide-scale use of ACTs in the absence of other proven malaria control interventions (e.g. IRS, ITNs). Since ACTs alone are not expected to be 100% effective in the control of malaria, other malaria control interventions should be implemented concurrently, and hence there will always be confounding factors when any one of the interventions is being evaluated. What is important is to ensure that evaluation studies for ACTs are appropriately designed so as to minimise the impact of other confounding factors on the results of the study. Such evaluations need to be undertaken for both low- , moderate- and high-intensity transmission settings, to explore the effect of intensity of malaria transmission on the extent to which ACTs reduce malaria transmission and delay antimalarial resistance.

- ★ There is need for more economic evaluations of the concurrent introduction of RDTs together with ACTs, particularly for more wide-scale implementation at national rather than at pilot level. This could be achieved through using an extended decision tree or Markov model that takes into consideration evaluation aspects for both ACTs and RDTs. In such models the inclusion of assumptions related to the benefits of improved health outcomes (e.g. of correctly treating non-malaria fevers) is important in most malaria endemic countries, where diarrhoea and pneumonia are large contributors to morbidity and mortality. Further, such evaluations should be comprehensive enough to measure the cost of policy change and wide scale implementation of RDTs and ACTs, and also the costs of treating non-malaria fever patients.

- ★ More comprehensive cost-effectiveness evaluation of rapid diagnostic tests (and other forms of malaria diagnosis) needs to be undertaken in various settings. Such evaluations should include all aspects of RDTs such as all the health outcomes associated with their use (including the resulting costs and outcomes of detecting true negatives that are then able to receive prompt treatment for other diseases, including changes in antibiotic use and resistance). In addition, cost-effectiveness studies of RDTs in future should take into consideration the important issues of sensitivity and specificity of RDTs, and how these aspects impact on the health outcomes associated with use of RDTs.

- ★ There is need for more economic evaluation studies of the concurrent introduction of RDTs together with ACTs, particularly for more wide-scale implementation at national level rather than at pilot level. This could be achieved through using an extended decision tree or Markov model that takes into consideration evaluation aspects for both ACTs and RDTs. In such models the inclusion of assumptions related to the benefits of improved health outcomes (of correctly treating non-malaria fevers) is important in settings such as Africa, where diarrhoea and pneumonia are large contributors to morbidity and mortality. Further, such evaluations should be comprehensive enough to measure the cost of policy change and wide scale implementation of RDTs and ACTs, and also the costs of treating non-malaria fever patients.

- ★ Lastly, given their acquisition costs, there is need for research in the area of sustainable financing for ACTs and RDTs, particularly in sub-Saharan Africa where they are needed most. Such research should explore the possibilities of financing of these two important interventions in the presence and absence of international donor funds.

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Annex 1: List of participants in Delphi Survey

1. BRIAN SHARP

Qualifications: PhD (epidemiology of malaria and malaria control)

Area of specialisation: Epidemiology and vector control

No. of years working on Malaria: 23 years

2. CHRIS CURTIS

Qualifications: PhD (genetics)

Area of specialisation: Malaria vector control

No. of years working on Malaria: 28 years

3. DAVID DURRHEIM

Qualifications: Medical, Public Health and Tropical Medicine - DrPH

Area of specialisation: Malaria Surveillance and control

No. of years working on Malaria: 10 years

4. KAREN BARNES

Qualifications: MBChB, MMed Clinical Pharmacology

Area of specialisation: Malaria Chemotherapy

No. of years working on Malaria: 9 years

5. MARLIES CRAIG

Qualifications: MSc (Parasitology, entomology)

Area of specialisation: Malaria Epidemiology, modelling, mapping, diagnosis

No. of years working on Malaria: 9 years

6. FRANCOIS NOSTEN

Qualifications: MD, PhD

Area of specialisation: Malaria Chemotherapy

No. of years working on Malaria: 17 years

7. RIC PRICE

Qualifications: MD, MRCP, MRCPath, Clinical ID and Tropical Research

Area of specialisation: Drug resistance and ACTs

No. of years working on Malaria: 10 years

8. BOB SNOW

Qualifications: MD, PhD

Area of specialisation: Malaria Epidemiology & Public Health

No. of years working on Malaria: 20 years

9. NICHOLAS WHITE

Qualifications: BSc Pharmacology, MBBS, MRCP (UK), MD, MA, FRCP, DSc Medicine

Area of specialisation: –Tropical Disease Chemotherapy and Drug Resistance

No. of years working on Malaria: 25 years

10. DID NOT RESPOND IN ANY ROUND

Annex 2: Questionnaire used for the Household Surveys

Excel File to be printed and attached.

SEACAT
EVALUATION
Ensuring Effective Malaria Treatment

HOUSEHOLD QUESTIONNAIRE
BASELINE EVALUATION
MPUMALANGA

QUESTIONNAIRE NUMBER:

Name of interviewer:			*(signature)* _____
Date of interview:	/ / 2001		
Start time:			
End time:			
Checked by Supervisor:	/ / 2001	h	*(signature)* _____
Coding checked:	/ / 2001	h	*(signature)* _____

Household Number:			
Area Name:			
Section Number:			
Magisterial District:			
Visit Number:	1	2	3

INTRODUCTION

[Enumerator: read the introductory statement over the page]

INFORMED CONSENT FOR INDIVIDUAL INTERVIEWS: HOUSEHOLD SURVEY

SMOG readability score: 20.48, 7th grade reading level

Introduction: My name is _____ and I am conducting a survey about malaria issues in Mpumalanga, on behalf of the Department of Health.
We are interested in learning what people do when they fall sick with malaria. We are interviewing many different households[1] in Tonga.

1 **Are you the female household head?** | yes | no |

NB: Preferably respondents should be female household heads. If the household head is not around, respondent must NOT be below the age of 18 years.

Purpose of the Research Study: This study will help inform the Mpumalanga Malaria Control Programme (MCP) as it plans malaria treatment. It will tell us how to better help malaria patients.

Procedures: If you agree to the study, a member of the research team will ask you questions about care you receive for malaria. They want to learn about what medicines / treatment you were given. Our questions should only take 60 minutes to answer.

Benefits: There is no direct benefit to you in being in the study, other than a chance to discuss what it is like when you are sick. The findings will help the MCP and health care workers to provide better care for you in future.

You do not have to answer any question that you do not want to. If you decide you do not want to join in this study, you are free to refuse. Not being in the study will have no effect on the care you receive at the clinic. If you agree to be in the study, you are free to stop at any point in time, with no consequences.

We will keep the data you give us private. Your answers will be put together with those of over 400 other households, so no one will be able to pick up what you or someone else said during the interview. We will not tell anyone if you agree or do not agree to be in the study, or if you choose to quit before it ends. Your name will not appear in any verbal or written report that comes out of the study. There are no right or wrong answers. Your open and honest opinion is important. If you do not understand a question, please tell me.

If, at any time, you have questions about this study, you may also contact Mr Aaron Mabuza, at the MPUMALANGA MALARIA CONTROL PROGRAMME OFFICES in Nelspruit, at this telephone number: **(013) 752 8085** or contact Dr Karen Barnes at the University of Cape Town: **(021) 406 6294.**

---

2 **Are you willing to be interviewed?*** | Yes | No |

Name: _____ **Signature:** _____

Date: _____ **Witness:** _____

** If 'NO' to the above question, thank them and do not interview that household.*

[1] Household defined as the people who live in the same house for 2 or more weeks each month, and share a common source of food.

SECTION 1: HOUSEHOLD CENSUS

ID no. (identifier code for each household member)	3 **Name** (enter first name only for each member) NB. Enter the name of the respondent first.	4 **Age** (in years)	5 **Gender** 1 = M 2 = F	6 **Relationship of members to the household head** 1 = Head 2 = Spouse / Wife 3 = Daughter / Son 4 = Grandchild 5 = Parent 6 = Grandparent 7 = Brother / Sister 8 = Other Relative 9 = Other 98 = DK	7 **What is the highest educational level of each person?** 1 = no schooling 2 = Creche - Grade 2 3 = Grade 3 - 7 4 = Grade 8 - 12 5 = Univ. Degree 6 = Diploma 7 = Vocational school 8 = Literacy training 9 = Other 98 = DK 99 = not applicable	8 **What is the occupation of each person listed?** 1 = Unemployed 2 = Subsistence farmer 3 = Agricultural labourer 4 = Non-agricultural labourer 5 = Skilled labourer / tradesman 6 = Small trader 7 = Civil servant 8 = Soldier 9 = Student 10 = Housewife 11 = Pensioner 12 = Other (specify) 98 = DK 99 = not applicable	9 **Are these persons full-time or part-time workers?** 1 = full-time 2 = part-time 98 = DK 99 = not applicable *[if full-time or NA, go to Q.11]*	10 **How many hours do the part-time workers work in a week?** (fill in hours per week for part-time workers) *or:* 98 = DK 99 = not applicable	11 **Has _____ ever suffered from malaria?** 1 = yes 2 = no 98 = DK *[if YES, fill in ID no & name at Q.14 (p.5) then continue census* *[if NO, fill in ID no & name at Q.71 (p.16) then continue census*
-1									
-2									
-3									
-4									
-5									
-6									
-7									
-8									
-9									
-10									
-11									
-12									

SECTION 2(a): MALARIA HISTORY & TREATMENT SEEKING BEHAVIOUR

12 What is the closest place you can get treatment when a household member is ill?

	Please tell me for...	Name of place	Type (eg. clinic / trad healer)	Usual mode of transport	Time taken to get there		Km (if known)	CODE
a)	Any medicines				*(hours)*	*(mins)*		
b)	Injections				*(hours)*	*(mins)*		
c)	Other treatment				*(hours)*	*(mins)*		

13 (a) **Do you have any medicines at home, for treating malaria?** | Yes | No | D/K | → *[If NO, skip to Q.14 next page]*

Could you please show me all the medicines you have at home, for treating malaria?

(b) *List all medicines that are mentioned / shown, and ask:* **What do you do with medicines?** *(dose, duration, in what circumstances?)*

	Name *(verify if shown)*	Description *(if not shown)*	Mentioned	Shown	What do you do with the medicines?	CODE
(i)			1	2		
(ii)			1	2		
(iii)			1	2		
(iv)			1	2		
(v)			1	2		
(vi)			1	2		
(vii)			1	2		
(viii)			1	2		
(ix)			1	2		

SECTION 2(b): DETAILS OF HOUSEHOLD MEMBERS WHO HAVE SUFFERED FROM MALARIA

	Fill in unique ID no & name during census ➡	**Member ID no:**			**Member ID no:**			**Member ID no:**		
	(ask Q.14-20 only after completing Sections 1 & 2 above)	**Name:**			**Name:**			**Name:**		
14	**When was the last time _____ had malaria?**	*(year)*	*(month)*		*(year)*	*(month)*		*(year)*	*(month)*	
15	**How did you know that _____ had malaria?**									
16	**During the last episode of malaria, did _____ seek any form of care?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
17	**Where did _____ seek care first?** *(type of place - eg. clinic, trad healer)*									
18	**What medicine did _____ receive / buy after seeking care?**									
19	**For how many days did _____ take the medicine?**			*(no of days)*			*(no of days)*			*(no of days)*
20	**Did _____ recover from the malaria after taking the medicines?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K

	Fill in unique ID no & name during census ➡	**Member ID no:**			**Member ID no:**			**Member ID no:**		
	(ask Q.14-20 only after completing Sections 1 & 2 above)	**Name:**			**Name:**			**Name:**		
14	**When was the last time _____ had malaria?**	*(year)*	*(month)*		*(year)*	*(month)*		*(year)*	*(month)*	
15	**How did you know that _____ had malaria?**									
16	**During the last episode of malaria, did _____ seek any form of care?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
17	**Where did _____ seek care first?** *(type of place - eg. clinic, trad healer)*									
18	**What medicine did _____ receive / buy after seeking care?**									
19	**For how many days did _____ take the medicine?**			*(no of days)*			*(no of days)*			*(no of days)*
20	**Did _____ recover from the malaria after taking the medicines?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K

21 Has any member of this household ever been admitted to hospital when suffering from malaria? | Yes | No | → *[If NO, skip to Q.31, next page]*

22 How many members have ever been admitted to hospital when suffering from malaria?

Now I want to ask you about the household member who was LAST admitted to hospital:

23 Can you recall when this household member was last admitted to hospital? *(month)* *(year)*

24 Which hospital was s/he admitted to? *(name of hospital)*

25 Had this household member sought care from somewhere else, before being admitted to hospital? | Yes | No | D/K | → *[If NO or D/K, skip to Q.29 below]*

26 Where had s/he sought initial care? *(circle applicable number/s)*

1	Public health centre / clinic	4	Malaria Camp	7	Care at home
2	Private GP / Private hospital	5	Traditional healer / Herbalist	8	Other *(specify)*:
3	Public Hospital	6	Drug shop / Chemist / Pharmacy	9	Don't know

27 What treatment or medicine did s/he receive at this INITIAL place? *(circle applicable number/s)*

1	CQ tablets	7	Quinine tablets	9	Aspirin tablets
2	SP tablets	6	Quinine injection	10	Herbal medicine
3	SP / CQ tablets	6	Quinine IV (drip)	11	Other *(specify)*:
4	CQ injection	8	Panado tablets	12	Don't know

28 Then what happened when s/he took this initial treatment?

29 What treatment or medicine did s/he receive at the hospital, where s/he was admitted? *(circle applicable number/s)*

1	CQ tablets	7	Quinine tablets	9	Aspirin tablets
2	SP tablets	6	Quinine injection	10	Herbal medicine
3	SP / CQ tablets	6	Quinine IV (drip)	11	Other *(specify)*:
4	CQ injection	8	Panado tablets	12	Don't know

30 How much money did you or the household spend on hospitalisation for this person? R

Now I need to ask you some questions about death in the family. Please remember that the purpose of this study is to try and improve the care for people with malaria, so that there is a better chance of curing illness and preventing death in future.

31 Has any member of this household ever died from malaria? | Yes | No | D/K | → *If NO or D/K: skip to Q.36 below*

32 *If YES:* How many people have died of malaria in this household? ____

Now I want to ask you about the household member who died MOST RECENTLY, due to malaria:

33 What was the gender of the household member who died of malaria? | M | F |

34 How old was the person when s/he died? *age in years:* ____

35 Would you be able to tell me anything more about what happened? (eg. had they gone to the clinic or hospital, had they received treatment, what medicine had they been given, had they taken all the treatment, what happened when they took the medicine, etc?)

SECTION 3: RECENT MALARIA EPISODES (Treatment seeking behaviour)

36 Would you please tell me, among the members of this household, who has had a malaria episode in the past ONE MONTH?

	Unique ID no:	Name:
(i)		
(ii)		
(iii)		
(iv)		

IMPORTANT INTERVIEWER NOTE:

☆ *If NO household member has had malaria in the past ONE MONTH, skip to Q.71 (Page 16)*

☆ *If more than one member of the household has had malaria in the past ONE MONTH, ask Q.37 - 70 for EACH person who has been with malaria in the past ONE month.*

☆ ***Questions 37 - 70 must be asked ONLY for household members who were identified as having had malaria in the past ONE month.***

(try to speak to the individual or their caregiver, but make sure you record the name and identification number of the person who was sick)

Member ID no:	**Name:**

		1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
37	**During the last episode of malaria, did _____ seek any form of care?** *[If NO, skip to Q.56, next page]*	Yes	No	D/K									
38	**(a) Where did s/he FIRST seek malaria treatment / care?** *[record name & type of place, and skip to Q.39 below]*												
	(b) Where did s/he NEXT seek malaria treatment / care? *[record name & type of place]*												
39	**How did s/he travel to the place where s/he received care?** *[record mode of transport most often used]*												
40	**How long did it take to get to the place of care?**	*(hours)*		*(mins)*		*(hours)*		*(mins)*		*(hours)*		*(mins)*	
41	**How much money did s/he spend on transport to go and seek care?**	R				R				R			
42	**Who went with him/her to the place where s/he sought care?**												
43	**How much money was spent on _____ (caregiver's) transport to go with the patient and seek care?**	R				R				R			
44	**What medicine did s/he receive or buy after seeking care?**												
45	**How much money did the medicine cost?**	R				R				R			
46	**Did any medicine remain after s/he had taken this malaria treatment?**	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
47	**Did s/he take all the medicine given?**	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
48	**When s/he sought care for malaria for the ____ time, how much did they charge for consultation / service fees?**	R				R				R			
49	**Did s/he have any malaria test done by the facility?** *[If NO or D/K, skip to Q.51, next page]*	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
50	**How much did she pay for the laboratory test?**	R				R				R			
51	**Thinking about all the money charged for consultations, medinines and tests, how much does s/he still have to pay?**	R				R				R			

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

	Member ID no:	Name:	1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
52	**What else did s/he (or the caregiver) spend money on while waiting for treatment (eg. food, drinks)** *[List all items in space provided; if nothing write N/A and skip to Q.54]*													
53	**How much money did they spend on these other items in total?**		R				R				R			
54	**Was s/he cured after taking this treatment?** *[If YES, skip to Q.57]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
55	*[If NO above]:* **Did s/he seek further treatment for malaria?** *[If sought further treatment, return to Q.38(b) - next column]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
56	*[If NO to Q.37 or Q.55]:* **Did s/he finally recover from the malaria without seeking additional treatment?**		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	

57	**How many days was s/he sick with malaria during the last episode of malaria?**	*no. days:*				
58	**Did s/he stop working / going to school during the period that s/he had malaria?** *[If NO, skip to Q.60]*	Yes	No	D/K		
59	*[If YES]:* **How many days did s/he NOT go to work / school during the last malaria episode?**	*no. days:*				
60	**Did someone do the work for him/her during the period when s/he was ill with malaria?** *[If NO, skip to Q.66]*	Yes	No	D/K		
61	**Who did the work for him/her during the time they were off sick?** *[write in name & relationship to patient]*	*name:*			*relationship:*	CODE
62	**How many days did this person not do their normal duties to do the work of the sick person?**	*no. days:*				
63	**Was s/he so sick that someone has to remain at home just to care for him / her?** *[If NO, skip to Q.50]*	Yes	No	D/K		
64	**Who cared for him/her during the time they were sick?** *[write in name & relationship to patient]*	*name:*			*relationship:*	CODE
65	**How many days did this person not do their normal duties to care for the sick person?**	*no. days:*				
66	*If hospitalisation already mentioned above, circle NA, and skip to Q.71 below* **Was the sick person admitted to hospital during the last malaria episode?** *[If NO, continue with next sufferer / Q.71]*	Yes	No	D/K	N/A → "N/A" = already mentioned	
67	**How did s/he travel to the hospital for admission?**					
68	**How much s/he spend on transport to the hospital for admission?**	R				
69	**Which hospital was s/he admitted to?**	*name:*				
70	**How much did s/he (or the household) pay for his/her hospitalisation?**	R				

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

☆ ***Questions 37 - 70 must be asked ONLY for household members who were identified as having had malaria in the past ONE month.***

(try to speak to the individual or their caregiver, but make sure you record the name and identification number of the person who was sick)

Member ID no:	Name:

		1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
37	During the last episode of malaria, did _____ seek any form of care? *[If NO, skip to Q.56, next page]*	Yes	No	D/K									
38	(a) Where did s/he FIRST seek malaria treatment / care? *[record name & type of place, and skip to Q.39 below]*												
	(b) Where did s/he NEXT seek malaria treatment / care? *[record name & type of place]*												
39	How did s/he travel to the place where s/he received care? *[record mode of transport most often used]*												
40	How long did it take to get to the place of care?	(hours)		(mins)		(hours)		(mins)		(hours)		(mins)	
41	How much money did s/he spend on transport to go and seek care?	R				R				R			
42	Who went with him/her to the place where s/he sought care?												
43	How much money was spent on _____ (caregiver's) transport to go with the patient and seek care?	R				R				R			
44	What medicine did s/he receive or buy after seeking care?												
45	How much money did the medicine cost?	R				R				R			
46	Did any medicine remain after s/he had taken this malaria treatment?	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
47	Did s/he take all the medicine given?	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
48	When s/he sought care for malaria for the ____ time, how much did they charge for consultation / service fees?	R				R				R			
49	Did s/he have any malaria test done by the facility? *[If NO or D/K, skip to Q.51, next page]*	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
50	How much did she pay for the laboratory test?	R				R				R			
51	Thinking about all the money charged for consultations, medinines and tests, how much does s/he still have to pay?	R				R				R			

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

CONTINUED....

	Member ID no:	Name:	1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
52	**What else did s/he (or the caregiver) spend money on while waiting for treatment (eg. food, drinks)** *[List all items in space provided; if nothing write N/A and skip to Q.54]*													
53	**How much money did they spend on these other items in total?**		R				R				R			
54	**Was s/he cured after taking this treatment?** *[If YES, skip to Q.57]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
55	*[If NO above]:* **Did s/he seek further treatment for malaria?** *[If sought further treatment, return to Q.38(b) - next column]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
56	*[If NO to Q.37 or Q.55]:* **Did s/he finally recover from the malaria without seeking additional treatment?**		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	

57	**How many days was s/he sick with malaria during the last episode of malaria?**	*no. days:*					
58	**Did s/he stop working / going to school during the period that s/he had malaria?** *[If NO, skip to Q.60]*	Yes	No	D/K			
59	*[If YES]:* **How many days did s/he NOT go to work / school during the last malaria episode?**	*no. days:*					
60	**Did someone do the work for him/her during the period when s/he was ill with malaria?** *[If NO, skip to Q.66]*	Yes	No	D/K			
61	**Who did the work for him/her during the time they were off sick?** *[write in name & relationship to patient]*	*name:*			*relationship:*		CODE
62	**How many days did this person not do their normal duties to do the work of the sick person?**	*no. days:*					
63	**Was s/he so sick that someone has to remain at home just to care for him / her?** *[If NO, skip to Q.50]*	Yes	No	D/K			
64	**Who cared for him/her during the time they were sick?** *[write in name & relationship to patient]*	*name:*			*relationship:*		CODE
65	**How many days did this person not do their normal duties to care for the sick person?**	*no. days:*					
66	*If hospitalisation already mentioned above, circle NA, and skip to Q.71 below* **Was the sick person admitted to hospital during the last malaria episode?** *[If NO, continue with next sufferer / Q.71]*	Yes	No	D/K	N/A	→	"N/A" = already mentioned
67	**How did s/he travel to the hospital for admission?**						
68	**How much s/he spend on transport to the hospital for admission?**	R					
69	**Which hospital was s/he admitted to?**	*name:*					
70	**How much did s/he (or the household) pay for his/her hospitalisation?**	R					

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

☆ ***Questions 37 - 70 must be asked ONLY for household members who were identified as having had malaria in the past ONE month.***

(try to speak to the individual or their caregiver, but make sure you record the name and identification number of the person who was sick)

Member ID no:	**Name:**

		1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
37	During the last episode of malaria, did _____ seek any form of care? *[If NO, skip to Q.56, next page]*	Yes	No	D/K									
38	(a) Where did s/he FIRST seek malaria treatment / care? *[record name & type of place, and skip to Q.39 below]*												
	(b) Where did s/he NEXT seek malaria treatment / care? *[record name & type of place]*												
39	How did s/he travel to the place where s/he received care? *[record mode of transport most often used]*												
40	How long did it take to get to the place of care?	*(hours)*		*(mins)*		*(hours)*		*(mins)*		*(hours)*		*(mins)*	
41	How much money did s/he spend on transport to go and seek care?	R				R				R			
42	Who went with him/her to the place where s/he sought care?												
43	How much money was spent on _____ (caregiver's) transport to go with the patient and seek care?	R				R				R			
44	What medicine did s/he receive or buy after seeking care?												
45	How much money did the medicine cost?	R				R				R			
46	Did any medicine remain after s/he had taken this malaria treatment?	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
47	Did s/he take all the medicine given?	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
48	When s/he sought care for malaria for the ____ time, how much did they charge for consultation / service fees?	R				R				R			
49	Did s/he have any malaria test done by the facility? *[If NO or D/K, skip to Q.51, next page]*	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
50	How much did she pay for the laboratory test?	R				R				R			
51	Thinking about all the money charged for consultations, medinines and tests, how much does s/he still have to pay?	R				R				R			

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

	Member ID no:	Name:	1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
52	**What else did s/he (or the caregiver) spend money on while waiting for treatment (eg. food, drinks)** *[List all items in space provided; if nothing write N/A and skip to Q.54]*													
53	**How much money did they spend on these other items in total?**		R				R				R			
54	**Was s/he cured after taking this treatment?** *[If YES, skip to Q.57]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
55	*[If NO above]:* **Did s/he seek further treatment for malaria?** *[If sought further treatment, return to Q.38(b) - next column]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
56	*[If NO to Q.37 or Q.55]:* **Did s/he finally recover from the malaria without seeking additional treatment?**		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	

57	**How many days was s/he sick with malaria during the last episode of malaria?**	*no. days:*				
58	**Did s/he stop working / going to school during the period that s/he had malaria?** *[If NO, skip to Q.60]*	Yes	No	D/K		
59	*[If YES]:* **How many days did s/he NOT go to work / school during the last malaria episode?**	*no. days:*				
60	**Did someone do the work for him/her during the period when s/he was ill with malaria?** *[If NO, skip to Q.66]*	Yes	No	D/K		
61	**Who did the work for him/her during the time they were off sick?** *[write in name & relationship to patient]*	*name:*			*relationship:*	CODE
62	**How many days did this person not do their normal duties to do the work of the sick person?**	*no. days:*				
63	**Was s/he so sick that someone has to remain at home just to care for him / her?** *[If NO, skip to Q.50]*	Yes	No	D/K		
64	**Who cared for him/her during the time they were sick?** *[write in name & relationship to patient]*	*name:*			*relationship:*	CODE
65	**How many days did this person not do their normal duties to care for the sick person?**	*no. days:*				
66	*If hospitalisation already mentioned above, circle NA, and skip to Q.71 below* **Was the sick person admitted to hospital during the last malaria episode?** *[If NO, continue with next sufferer / Q.71]*	Yes	No	D/K	N/A →	"N/A" = already mentioned
67	**How did s/he travel to the hospital for admission?**					
68	**How much s/he spend on transport to the hospital for admission?**	R				
69	**Which hospital was s/he admitted to?**	*name:*				
70	**How much did s/he (or the household) pay for his/her hospitalisation?**	R				

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

☆ ***Questions 37 - 70 must be asked ONLY for household members who were identified as having had malaria in the past ONE month.***

(try to speak to the individual or their caregiver, but make sure you record the name and identification number of the person who was sick)

Member ID no:	**Name:**

		1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
37	**During the last episode of malaria, did _____ seek any form of care?** *[If NO, skip to Q.56, next page]*	Yes	No	D/K									
38	**(a) Where did s/he FIRST seek malaria treatment / care?** *[record name & type of place, and skip to Q.39 below]*												
	(b) Where did s/he NEXT seek malaria treatment / care? *[record name & type of place]*												
39	**How did s/he travel to the place where s/he received care?** *[record mode of transport most often used]*												
40	**How long did it take to get to the place of care?**	*(hours)*		*(mins)*		*(hours)*		*(mins)*		*(hours)*		*(mins)*	
41	**How much money did s/he spend on transport to go and seek care?**	R				R				R			
42	**Who went with him/her to the place where s/he sought care?**												
43	**How much money was spent on _____ (caregiver's) transport to go with the patient and seek care?**	R				R				R			
44	**What medicine did s/he receive or buy after seeking care?**												
45	**How much money did the medicine cost?**	R				R				R			
46	**Did any medicine remain after s/he had taken this malaria treatment?**	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
47	**Did s/he take all the medicine given?**	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
48	**When s/he sought care for malaria for the ____ time, how much did they charge for consultation / service fees?**	R				R				R			
49	**Did s/he have any malaria test done by the facility?** *[If NO or D/K, skip to Q.51, next page]*	Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
50	**How much did she pay for the laboratory test?**	R				R				R			
51	**Thinking about all the money charged for consultations, medinines and tests, how much does s/he still have to pay?**	R				R				R			

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

	Member ID no:	Name:	1st malaria treatment			CODE	2nd malaria treatment			CODE	3rd malaria treatment			CODE
52	What else did s/he (or the caregiver) spend money on while waiting for treatment (eg. food, drinks) *[List all items in space provided; if nothing write N/A and skip to Q.54]*													
53	How much money did they spend on these other items in total?		R				R				R			
54	Was s/he cured after taking this treatment? *[If YES, skip to Q.57]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
55	*[If NO above]:* Did s/he seek further treatment for malaria? *[If sought further treatment, return to Q.38(b) - next column]*		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	
56	*[If NO to Q.37 or Q.55]:* Did s/he finally recover from the malaria without seeking additional treatment?		Yes	No	D/K		Yes	No	D/K		Yes	No	D/K	

57	How many days was s/he sick with malaria during the last episode of malaria?	*no. days:*				
58	Did s/he stop working / going to school during the period that s/he had malaria? *[If NO, skip to Q.60]*	Yes	No	D/K		
59	*[If YES]:* How many days did s/he NOT go to work / school during the last malaria episode?	*no. days:*				
60	Did someone do the work for him/her during the period when s/he was ill with malaria? *[If NO, skip to Q.66]*	Yes	No	D/K		
61	Who did the work for him/her during the time they were off sick? *[write in name & relationship to patient]*	*name:*			*relationship:*	CODE
62	How many days did this person not do their normal duties to do the work of the sick person?	*no. days:*				
63	Was s/he so sick that someone has to remain at home just to care for him / her? *[If NO, skip to Q.50]*	Yes	No	D/K		
64	Who cared for him/her during the time they were sick? *[write in name & relationship to patient]*	*name:*			*relationship:*	CODE
65	How many days did this person not do their normal duties to care for the sick person?	*no. days:*				
66	*If hospitalisation already mentioned above, circle NA, and skip to Q.71 below* Was the sick person admitted to hospital during the last malaria episode? *[If NO, continue with next sufferer / Q.71]*	Yes	No	D/K	N/A →	"N/A" = already mentioned
67	How did s/he travel to the hospital for admission?					
68	How much s/he spend on transport to the hospital for admission?	R				
69	Which hospital was s/he admitted to?	*name:*				
70	How much did s/he (or the household) pay for his/her hospitalisation?	R				

APPROPRIATE BOX MUST BE TICKED ON EVERY PAGE: ☐ *Completed for household member* ☐ *Not applicable*

SECTION 4: FEVER HISTORY & TREATMENT SEEKING BEHAVIOUR

☆ ***Questions 71 - 80 must be asked ONLY for household members who have NEVER suffered from malaria. If ALL members have had malaria, skip to Section 5.***

	Fill in unique ID no & name during census ➡	**Member ID no:**			**Member ID no:**			**Member ID no:**		
	(ask Q.71 - 80 only after completing Sections 1-3 above)	**Name:**			**Name:**			**Name:**		
71	**Has _____ experienced an illness with fever in the past 4 weeks?** *[If NO, go to next member]*	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
72	**Are you or is _____ still having the fever?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
73	**What other symptoms accompanied the fever?**									
74	**What medicine did _____ try at home?** *[If NONE, circle (1) then skip to Q.80]*	1	None		1	None		1	None	
		2	CQ tablets →	*ask Q.75*	2	CQ tablets →	*ask Q.75*	2	CQ tablets →	*ask Q.75*
		3	SP tablets →	*ask Q.75*	3	SP tablets →	*ask Q.75*	3	SP tablets →	*ask Q.75*
		4	Quinine tablets →	*ask Q.75*	4	Quinine tablets →	*ask Q.75*	4	Quinine tablets →	*ask Q.75*
		5	Panado tablets		5	Panado tablets		5	Panado tablets	
		6	Asprin tablets		6	Asprin tablets		6	Asprin tablets	
		7	Traditional medicine		7	Traditional medicine		7	Traditional medicine	
		98	Don't know		98	Don't know		98	Don't know	
		8	Other (specify):		8	Other (specify):		8	Other (specify):	
75	*If there is any anti-malarial listed for Q.74, ask:* **Where did _____ get the medicines?**									
76	**How many days after the fever began did _____ start this treatment?**			*(no of days)*			*(no of days)*			*(no of days)*
77	**For how many days did _____ continue to take this treatment?**			*(no of days)*			*(no of days)*			*(no of days)*
78	**What was the total cost of this treatment (in rands?)**	R			R			R		
79	**Did ______ recover from the malaria after taking the medicines?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
80	*If 'None' in Q.74 or 'No' in Q.79, ask:* **Where did _____ seek treatment for the fever?**									

SECTION 4: (continued)

☆ ***Questions 71 - 80 must be asked ONLY for household members who have NEVER suffered from malaria. If ALL members have had malaria, skip to Section 5.***

	Fill in unique ID no & name during census ➡	**Member ID no:**			**Member ID no:**			**Member ID no:**		
	(ask Q.71 - 80 only after completing Sections 1-3 above)	**Name:**			**Name:**			**Name:**		
71	**Has _____ experienced an illness with fever in the past 4 weeks?** *[If NO, go to next member]*	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
72	**Are you or is _____ still having the fever?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
73	**What other symptoms accompanied the fever?**									
74	**What medicine did _____ try at home?** *[If NONE, circle (1) then skip to Q.80]*	1 2 3 4 5 6 7 98 8	None CQ tablets → SP tablets → Quinine tablets → Panado tablets Asprin tablets Traditional medicine Don't know Other (specify):	 *ask Q.75* *ask Q.75* *ask Q.75*	1 2 3 4 5 6 7 98 8	None CQ tablets → SP tablets → Quinine tablets → Panado tablets Asprin tablets Traditional medicine Don't know Other (specify):	 *ask Q.75* *ask Q.75* *ask Q.75*	1 2 3 4 5 6 7 98 8	None CQ tablets → SP tablets → Quinine tablets → Panado tablets Asprin tablets Traditional medicine Don't know Other (specify):	 *ask Q.75* *ask Q.75* *ask Q.75*
75	*If there is any anti-malarial listed for Q.74, ask:* **Where did _____ get the medicines?**									
76	**How many days after the fever began did _____ start this treatment?**			*(no of days)*			*(no of days)*			*(no of days)*
77	**For how many days did _____ continue to take this treatment?**			*(no of days)*			*(no of days)*			*(no of days)*
78	**What was the total cost of this treatment (in rands?)**	R			R			R		
79	**Did _____ recover from the malaria after taking the medicines?**	Yes	No	D/K	Yes	No	D/K	Yes	No	D/K
80	*If 'None' in Q.74 or 'No' in Q.79, ask:* **Where did _____ seek treatment for the fever?**									

SECTION 5: HOUSEHOLD SOCIO-ECONOMIC PROFILE & ASSETS

81 About how much of your household's food do you grow yourself?

1	Very little / none
2	About half
3	Almost all
4	Don't know

82 About how much money does your household spend per month on food?

(not including food grown by the household)

R

83 About how much money does your household spend on the following items, in Rand:

Transport - **per month**	R
Electricity/ other fuel sources (eg. paraffin) - **per month**	R
Water - **per day**	R
Rent (if house is rented) - **per month**	R

84 What is the MAIN source of water for this household?

1	Piped (tap) water, in dwelling	6	Borehole (communal)
2	Piped (tap) water, on site or in yard	7	Rain water tank on site
3	Public tap	8	Flowing water / stream
4	Water carrier or tanker	9	Dam / pool / stagnant water
5	Borehole on site	10	Well / spring
11	Other *(specify):*		

continue on same page at top of next column, Q.85

85 What is the MAIN source of enery / fuel used for cooking by this household?

1	Electricity	5	Wood
2	Gas	6	Animal dung
3	Paraffin	7	Solar energy
4	Coal	8	Other *(specify):*

86 What type of toilet facility is available for this household?

1	Flush toilet (in dwelling)	5	Other pit latrine
2	Flush toilet (on / off site)	6	Bucket toilet
3	Chemical toilet (on / off site)	7	None
4	Pit latrine with ventilation (VIP)		

87 Could you tell me if someone in your household owns any of the following, and how many of each: *NB: In each category, indicate the number of items owned. If household does not have an item, enter zero.*

ANIMALS	No.	HOUSEHOLD GOODS	No.
(a) Chickens		(g) Radio	
(b) Goats		(h) Television	
(c) Sheep		(i) Tractor	
(d) Cows		(j) Fridge	
(e) Pigs		(k) Bicycle	
(f) Other animals *(specify):*		(l) Car	

[copy ID & names from census page, and fill in below] ↓ ID no.	First name	88 What is the average monthly income of _____ (each member) [Fill in amount in Rand. If not employed or student, fill in zero]	89 Does _____ (each member) receive additional income from other sources? (eg. sale of agricultural produce, money sent sent by family living elswhere)			90 If YES in Q.89 ask: How much money does _____ receive from other sources each month, on average?
-1		R	Yes	No	D/K	R
-2		R	Yes	No	D/K	R
-3		R	Yes	No	D/K	R
-4		R	Yes	No	D/K	R
-5		R	Yes	No	D/K	R
-6		R	Yes	No	D/K	R
-7		R	Yes	No	D/K	R
-8		R	Yes	No	D/K	R
-9		R	Yes	No	D/K	R
-10		R	Yes	No	D/K	R
-11		R	Yes	No	D/K	R
-12		R	Yes	No	D/K	R

This is the end of our interview. Thank you very much for your time and assistance.

_____ (Time ended)

DEBRIEFING *(interviewer, please observe and fill in the following)*

91 Type of walls of house

1	Reeds	4	Mud or mud bricks
2	Canvas	5	Fire bricks
3	Cement blocks	6	Stone / cement
		7	Other *(specify)*: _____

92 Type of walls of house

1	Thatch	4	Canvas
2	Tile	5	Asbestos
3	Corrugated iron sheets	6	Other *(specify)*: _____

93 Please describe the mood of the respondent for the period of the interview

_____

_____

_____

94 How many other adults were present during the interview? ____

95 Did any of these other people contribute to the interview, other than the respondent? Yes | No

96 Any other observations? Or comments from debriefing?

_____

_____

_____

ADDITIONAL NOTES / RESPONSES

Please record any additional information or relevant "stories" which are not captured by the questionnaire.
(Be sure to reference all notes with the relevant Question Number.

Q.no	Comment

Annex 3: Questionnaire used for Delphi Survey

SEACAT / LSDI DELPHI SURVEY: Round 1

How have various factors contributed to the decline in Malaria morbidity and mortality observed in Kwazulu Natal in the past two years?

Thank you for your willingness to participate in this Delphi Survey. Your opinions are highly valued and your time in participating is appreciated. We estimate that it should take you 15 to 30 minutes to complete this questionnaire. The information you will provide will be treated with confidentiality, and you will be provided with an anonymous summary of results at the end of each round of the survey. You do not have to fill in your name anywhere on this questionnaire.

INTRODUCTION

We would greatly appreciate your participation in our survey of expert opinion using the Delphi Technique, to explain the remarkable decrease in malaria morbidity and mortality between 2000 and 2001 observed in northern Kwazulu Natal (KZN) namely:

80% decrease in the number of confirmed malaria cases,

82% decrease in hospital malaria admissions,

88% decrease in malaria related deaths and

case fatality decrease from 0.81 in 2000 to 0.46 in 2001 (RR0.61; 0.41-0.91)

Additional background information is in the other 3 worksheets of this document.

This survey is made up Of THREE sections.

SECTION 1 will ask for your opinions about and estimates of trends in MALARIA MORBIDITY AND MORTALITY in KZN had there not been a change in indoor residual spraying (IRS) in KZN to spraying traditional structures with DDT; introducing IRS in Southern Mozambique, and introduction of Coartem as first line treatment for malaria in KZN.

SECTION 2 will ask for your opinions on and estimates of the breakdown of the contribution of various factors to the differences between what would have happened had no intervention occurred and the observed changes in malaria incidence and related health outcomes.

SECTION 3 will ask for your estimates of probabilities for different health outcomes related to malaria treatment at health facility level.

You are kindly requested to provide, to the best of your knowledge and expertise, answers/estimates to the questions. ***If you feel that you cannot make any contribution to a specific section/question, enter D/K (don't know) and proceed to the next section/question.***

Please complete this questionnaire in the Excel spreadsheet provided and return it by 16 June 2003 at the latest to muhekic@heu.uct.ac.za

SECTION 1

Background local information:

IRS with pyrethroids replaced DDT in 1996. Pyrethroid resistant Anopheles funestus, a vector which had not been detected for many decades previously, was discovered in December 1999 in northern Kwazulu Natal; a considerable proportion was sporozoite positive. This resulted in a change back to spraying with DDT in 2000.

SP parasitological failure increased from 23.5% at 28 days in 1996 (20.6% RI + 2.9% RIII) to 88% at 42 days in 2000 (35% RI + 40% RII + 12% RIII). In 2000 52% of in vivo study patients carried gametocytes 14 days after treatment with SP.

The notified Malaria Case Fatality ratio was 0.81 in 2000

Comparing sentinel hospital and clinic data with notification data suggests that under notification was markedly exaggerated by the peak of the epidemic in 2000.

The total population living in malaria risk areas (assuming no change in malaria control interventions) far exceeds 2 million.

There is a lot of cross-border movement between Southern Mozambique and Northern Kwazulu Natal, particularly moving from Mozambique to do shopping and to seek medical care in South Africa. Until 2000, there was no vector control in Mozambique. It is believed that there were numerous IMPORTED malaria cases from Mozambique until 2000.

Assuming that the following changes did NOT take place in KZN/Mozambique;(1) change in IRS in KZN to spraying traditional structures with DDT; (2) introduction of indoor residual spraying in Southern Mozambique; and (3) introduction of Coartem as first line treatment in KZN.

Question 1.1: What, in your opinion, do you think would have happened in terms of malaria morbidity and mortality in KZN, over the 5 year period (2001-2005)? ***Give description below***.

Don't Know (DK)

Question 1.2: Based on the confirmed malaria case NOTIFICATIONS for KZN for 1996-2000 provided below, provide estimates of malaria cases and deaths for 2001 - 2005, assuming that SP resistance levels continued to grow.

	1996	1997	1998	1999	2000
(I) Number of notified confirmed malaria cases	10,535	11,425	14,575	27,238	42,284
(ii) Number of notified confirmed malaria deaths	32	38	112	214	342

	2001	2002	2003	2004	2005	
(I) Your estimated number of malaria cases						DK
(ii) Your estimated number of malaria deaths						DK

Note: BACKGROUND INFORMATION

Based on extrapolation of a model based on 30 years of notification data in Kwazulu Natal developed by Craig M et al (submitted), assuming no changes in malaria control interventions or climatic changes the following notification rates are predicted:.

2001	2002	2003	2004	2005
53,100	77,507	113,133	165,135	241,040

Question 1.3: It would be helpful if you could briefly comment on how you reached the estimates you provided in question 1.2 above.

Question 1.4: Is there evidence of relevance to the above questions that you would like the Delphi Survey panellists to consider prior to the next survey round? *Please provide it in the space below.*

SECTION 2

Background local information:

Malaria in Kwazulu Natal is confined to areas bordering on neighbouring Mozambique, and there is substantial population migration between Mozambique and northern Kwazulu Natal.

There were some climatic changes around 2000-2001 would have contributed to a decline in the number of malaria cases. However, a consensus panel agreed that this would only have created a temporary fluctuation on the overall trend.

In vivo study of Coartem (artemether-lumefantrine) therapeutic efficacy in 2002 found 99% parasitological cure at 42 days, and 1% RI failure (on day 28)

No patients without gametocytes on Day 0 developed gametocytes following treatment with Coartem. All patients cleared gametocytes by Day 14. As both duration of gametocyte carriage and gametocyte density influence transmission, the area under the gametocyte time curve (AUC) were calculated. Following SP the mean gametocyte AUC was 3898 gametocytes per microlitre per person week, compared with 31 gametocytes per microlitre per person week following Coartem ($p<0.001$).

Insecticide treated bed nets were introduced as a controlled study in 5700 household members in 1998, and are sold by the MOH (around USD 2.50) but coverage is generally very low.

Malaria admission rates in 3 sentinel sites vary between 10-18% of NOTIFIED malaria cases.

Question 2.1: In your opinion, what factors are responsible for the observed dramatic decline in malaria incidence in KZN in 2001 and 2002 relative to what would have happened had there been no changes in malaria control interventions? If there are other contributory factors, please add them. Please rank each in order of significance.

Factor	**Ranking** (e.g. 1 for most important, ...5 least important)	
a. Household spraying with DDT (to which A. funestus is sensitive) for traditional structures but continued pyrethroid spraying for western structures in northern KZN in March 2000 (**DDT in KZN**)		DK
b. Introduction of Indoor Residual Household spraying in Southern Mozambique in October 2000 (**IRS-Moz**)		DK
c. Effects of introduction of Artemisinin-based combination therapy as 1st line treatment in January 2001 (**Coartem**), both in terms of increasing parasitological cure rates (by 87%) and by decreasing gametocyte carriage (quantified above)		DK
d. Climatic changes		DK
e.		DK
f.		DK
g.		DK
h.		DK

Question 2.2: In your opinion, how much do you think the above factors have contributed to the specific health outcomes below? Please indicate (in terms of % contribution) the extent to which you think the factors listed above have contributed to the differences between what would have occurred without the three malaria control interventions listed above and those observed :

NOTE: Percentages in EACH row (below) should add up to 100.

	DDT in KZN %	IRS-Moz %	Coartem %	Climate %	Factor (e) %	Factor (f) %	Factor (g) %	Factor (h) %
1. Reduction in malaria cases								
2. Reduction in malaria admissions								
3. Reduction in malaria deaths								

Question 2.3: In your opinion, what methods could be used prospectively in other sites where both ACT and improved vector control are soon to be introduced in quick succession, to validate the proportional contribution of each factor, and describe to any interactions between these factors.

DK

Question 2.4: It would be helpful if you could briefly comment on the basis for the ranking and estimates you provided in questions 2.1 and 2.2 above.

Quesiton 2.5: Is there evidence available of relevance to the above questions that you would like the Delphi Survey panelists to consider prior to the next survey round?

SECTION 3

Question 3.1: What is the probability of uncomplicated malaria progressing to death without any antimalarial treatment?

DK

Question 3.2: What is the probability of malaria DEATH in a patient who initially failed SP (for RI, RII and RIII parasitological failure by 42 days) without any further antimalarial treatment?

RI	RII	RIII	
			DK

Question 3.3: What is the probability of malaria DEATH in a patient who initially failed AL (for RI, RII and RIII parasitological failure by 42 days) without any further antimalarial treatment?

RI	RII	RIII	
			DK

Question 3.4: Are there any additional comments you would like to make on Section 3?

Question 3.5: Is there evidence available of relevance to the above questions that you would like the Delphi Survey panellists to consider prior to the next survey round?

Kindly provide the following information. This information will be treated with confidentiality.

Your academic background/specialisations	
Area of specialisation on Malaria matters	
Number of years working on Malaria	

Thank you again for your participation

Please return your questionnaire to Charlotte Muheki by email (muhekic@heu.uct.ac.za). Kindly return responses NOT LATER THAN 16th June 2003.