A COST ANALYSIS OF THE TREATMENT OF FIRST-LINE UNCOMPLICATED MALARIA IN THE TONGA DISTRICT OF MPUMALANGA

by

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Abstract

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Following the completion of a detailed baseline study of malaria in the region, a model was developed to assess the cost-effectiveness of switching from chloroquine to sulfadoxine-pyrimethamine as first line treatment in the Tonga district of Mpumalanga, South Africa, where malaria is seasonal and the population is non-immune. *In vivo* drug resistance was used to create a resistance variable, which was used to assess the 1997 relative costs to the health care system of employing the two drugs, analysing factors such as drug costs, staff time, transport costs, maintenance costs, utility costs, training costs and consumables costs to generate an average cost-effectiveness ratio. The model was subsequently used to estimate the average cost-effectiveness ratios of nine other potential agents for the treatment of first line malaria, including artesunate monotherapy, artesunate combinations, pyronaridine, atovaquone-proguanil, co-artemether, halofantrine, amodiaquine, and mefloquine. It was found that sulfadoxine-pyrimethamine was 5 times more cost-effective as first line therapy than chloroquine. Of the other modelled drugs, it was recommended that an artesunate combination should be implemented when it becomes necessary to replace sulfadoxine-pyrimethamine; artesunate-mefloquine and artesunate-SP were estimated to be 6 times and 9 times as cost-effective as chloroquine, respectively.

Multilateral Initiative on Malaria

This work was presented and subjected to peer review at the Economics of Malaria breakaway group at the MIM African Malaria Conference in Durban, South Africa, on Monday 15 March 1999.

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This manuscript was prepared using Microsoft Word 97. Microsoft Excel 97 was used for all spreadsheet calculations and the majority of charts. An evaluation version of Palisade @Risk 3.5.2 was used for risk analysis and simulation. Microsoft Access 97 was the database of choice. StatSoft Statistica 5.0 was used for some statistical calculations. GraphPad Prism 2.01 was used for the creation of some charts, as well as some statistical calculation. Chemical structures were drawn using MDL ISIS/Draw 2.1.3d. Some illustrations and maps were created with CorelDRAW 8.0.

Chapter 1

INTRODUCTION & LITERATURE REVIEW

1.1. Malaria

Malaria results from infection by one or more of the four species of the protozoal genus *Plasmodium*. Infection in the field is generally facilitated by the bite of the disease's vector, mosquitoes of the *Anopheles* genus, but may result from any direct transfer of contaminated blood. At any one time it infects more than one third of the world's population, mostly in the third world. More than 400 million cases of *Plasmodium falciparum* malaria occur globally every year, and 2 million children die (World Health Organisation, 1994). In sub-Saharan Africa, more than 15% of disability-adjusted life years (DALYs) lost annually are lost to malaria morbidity and mortality (Foster & Phillips, 1998).

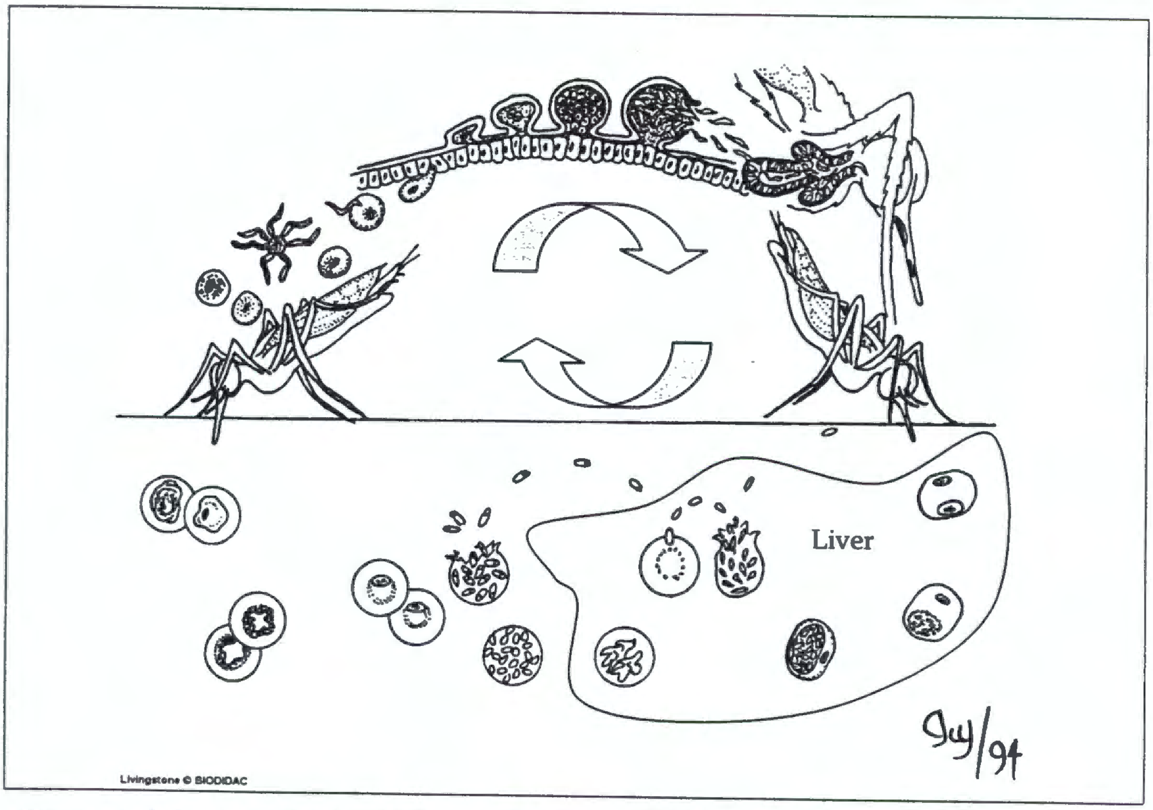
P. falciparum and *P. malariae* have a single cycle of liver cell invasion, which differentiates them from the other two species, *P. vivax* and *P. ovale*. The latter two may become dormant in hepatic cells, subsequently resulting in occasional relapses. *P. falciparum* and *P. malariae*, however, may only replicate in red blood cells. Of the four, *P. falciparum* is the most dangerous, and may be lethal if not treated correctly and promptly (Boyce, 1997).

During a blood meal, an infected *Anopheles* mosquito transmits between 5 and 100 motile, unicellular sporozoites into the bloodstream of the organism upon which it is feeding. These rapidly migrate to the liver and gain access to hepatocytes, where they divide, eventually forming mature liver schizonts containing 2 000 to 40 000 uninucleate daughter merozoites. After 6 to 16 days, the schizonts rupture and 10^5 to 10^6 merozoites are released into the bloodstream. The merozoites rapidly invade red blood cells to form ring-shaped trophozoites, which differentiate into mature red cell schizonts within 48 hours (in *P. falciparum*, *P. ovale*, and *P. vivax*) or 72 hours (in *P. malariae*). Finally, between 6 and 24 new daughter merozoites are released to continue the reproduction cycle (see figure). *P. vivax* and *P. ovale* have a preference for reticulocytes, while *P. malariae* preferentially attacks senescent erythrocytes, with the result that parasitaemia rarely exceeds 2%. However, *P. falciparum*, despite preferring reticulocytes, will invade all red blood cells, accounting for the substantially higher mortality found in those infected with it. Parasitaemia may exceed 50% in exceptional cases (Stanley, 1998).

Also formed during the parasitic life cycle are sexual forms called gametocytes, which are differentiated from merozoites. Gametocytes circulate asymptomatically for months or years until they are ingested by anopheline mosquitoes, upon which they form large numbers of infective sporozoites in the mosquito midgut over a period of 8 to 35 days. The sporozoites migrate to the mosquito's salivary glands and the cycle begins anew (Stanley, 1998).

Once infected by the parasite, an incubation period of between 10 and 35 days follows. Initial symptoms are non-specific, and the disease is often misdiagnosed as the common cold or influenza. Low-grade fever, headache, malaise, fatigue, abdominal discomfort, myalgia, and chills present, and last 2-3 days. A sequential pattern of attacks will then appear: a 48-hourly (or 72-hourly in *P. malariae* infections) periodic cycle of rigors, fever, and sweating. Symptoms occur due to the release of tumor necrosis factor (TNF-α) and inflammatory cytokines, which is in turn caused by cyclical red blood cell lysis (Stanley, 1998).

In *P. falciparum*, additional complications may arise, including cerebral malaria, which includes symptoms of headache, mental disturbance, neurological signs, convulsions, delirium, and coma. Other symptoms include hyperpyrexia, haemolytic anemia, noncardiogenic pulmonary oedema, acute tubular necrosis and renal failure with concomitant dark urine production (blackwater fever), acute hepatopathy with centrilobular necrosis and jaundice, hypoglycaemia, adrenal insufficiency-like syndrome, cardiac dysrhythmias, gastrointestinal upset including secretory diarrhoea and dysentery, and fluid and electrolyte imbalance (Boyce, 1997).



Livingstone © BIODIDAC

Figure 1.1. Life cycle of the malaria parasite. (Image © BIODIDAC. Used with permission. See http://biodidac.bio.uottawa.ca/.) Modified to show direction of the cycle and location of the liver.

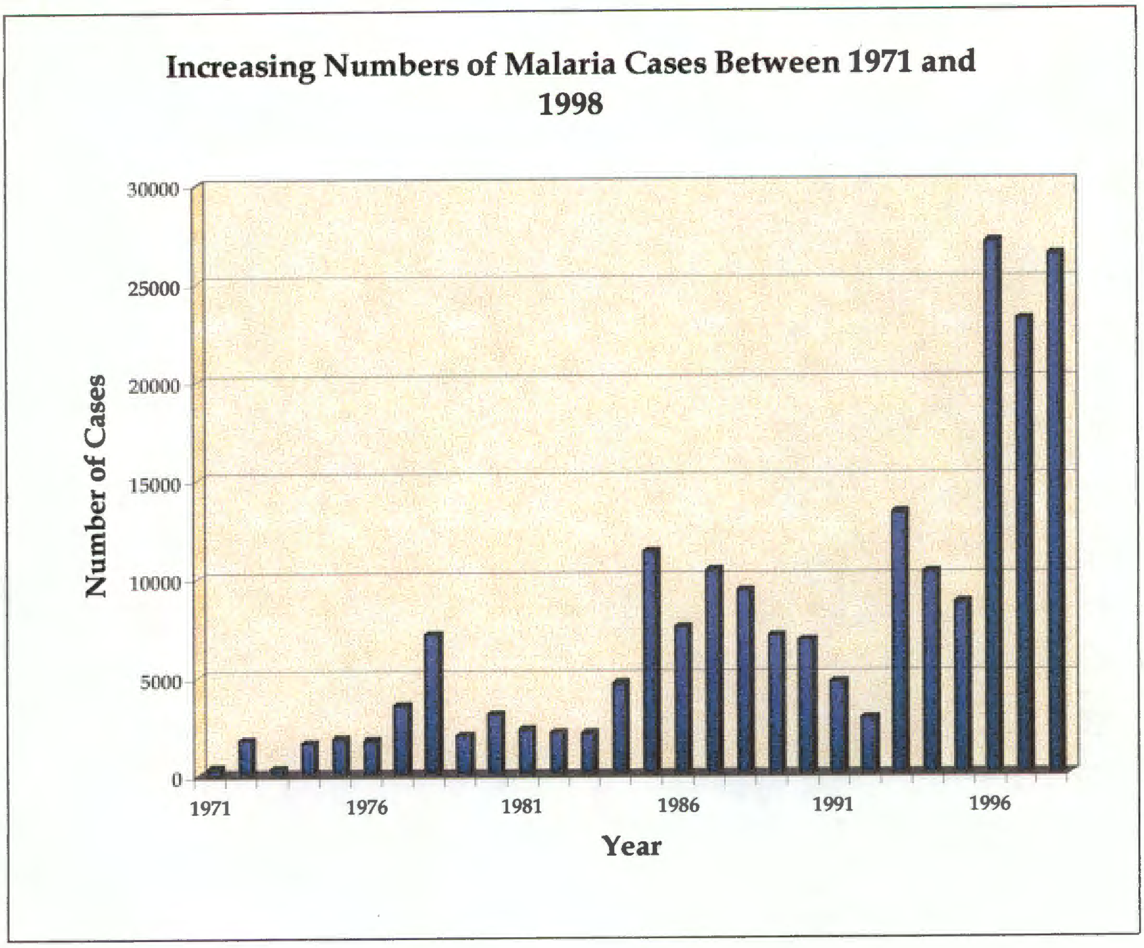


Figure 1.2. Increase in laboratory-confirmed malaria cases in South Africa between 1971 and 1998. Data presented with permission of D Lombaard of the Division of Vector-Borne Diseases at the South African Department of Health.

1.2. Malaria in Southern Africa

Malaria infects 5% of the world's population at any one time; in Africa, the disease accounts for the largest number of lost disability-adjusted life years (DALYs) on the continent, a total of 32 million in 1990 (Murray *et al*, 1994). 90% of the 1.5-million malaria deaths worldwide per annum occur in sub-Saharan Africa, mostly in children: 68% of fatalities in 1990 were under the age of four (Murray *et al*, 1994; le Sueur *et al*, 1996). In South Africa, the situation is worsening rapidly, with a large increase in cases and deaths over the past five years, reflected in official notification data from the Department of Health. This increase may be explained by increased rainfall, increased migration and developing resistance to chloroquine.

Malaria accounts for 10%-30% of all new hospital admissions in Sub-Saharan Africa. Malaria was also responsible for the loss of 35.4 million disability-adjusted life years (DALYs) to the world in 1990, which was 2.6% of the global total. In Sub-Saharan Africa, malaria accounted for 10.8% of the regional total of lost DALYs (Murray *et al*, 1994).

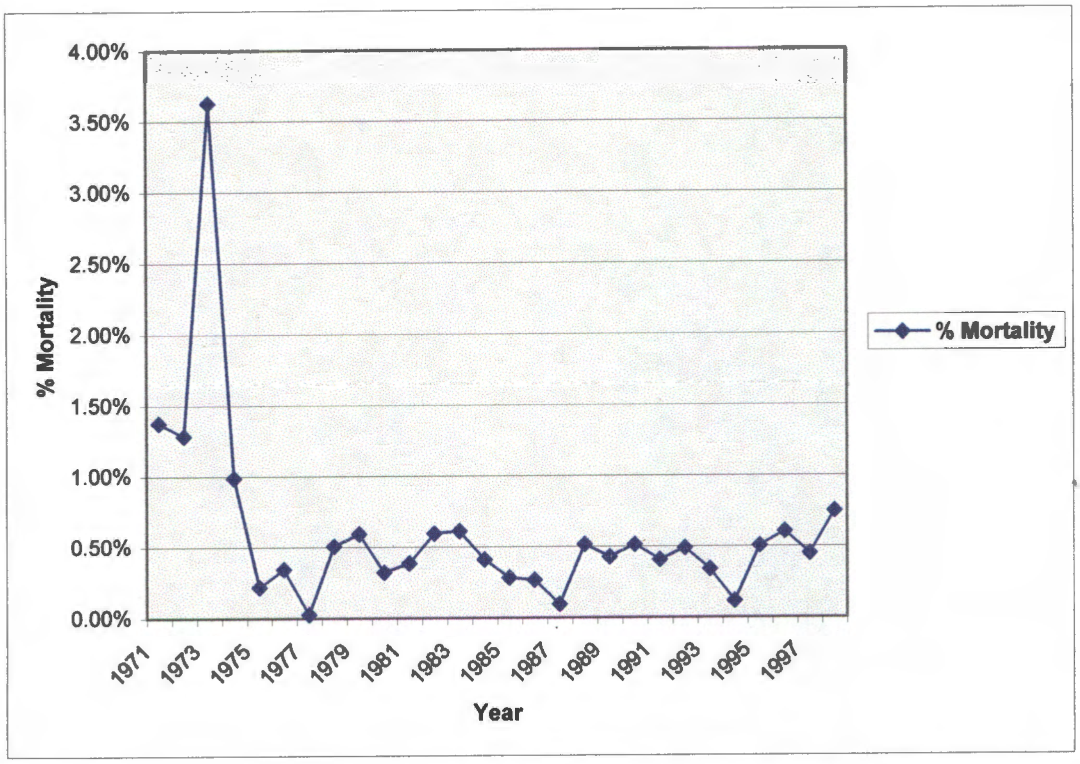


Figure 1.3. Percentage malaria mortality in South Africa from 1971 to 1998. Data presented with permission of D Lombaard of the Division of Vector-Borne Diseases at the South African Department of Health. These figures may be an under-estimate, owing to under-reporting of deaths.

1.3. Malaria in South Africa

Malaria in South Africa is confined to KwaZulu-Natal, Mpumalanga and Northern Province. Most cases (about 95%) are the result of infection by *Plasmodium falciparum*, the most dangerous malarial agent, with the balance being composed of *Plasmodium ovale* and *Plasmodium malariae* infections (Sharp & le Sueur, 1996; Murray *et al*, 1994). Figure 1.2 and Figure 1.3 illustrate the increasing number of cases in recent years and the mortality associated with this.

The principle vector for the disease in South Africa is *Anopheles arabiensis*, a common species of mosquito in the border areas. Malaria is transmissible by most Anopheline mosquitoes, but other species have been all but eradicated by an exhaustive vector control programme. *A. arabiensis* has survived best due to its so-called 'hut-leaving' behaviour in the presence of DDT (Sharp *et al*, 1990).

An effective vector control programme has led to an overall reduction in size of the malaria-endemic areas within South Africa's borders since peak infection rates recorded in the 1930s, but in recent years these areas have been encroaching once more, with total annual cases steadily increasing (Sharp & le Sueur, 1996).

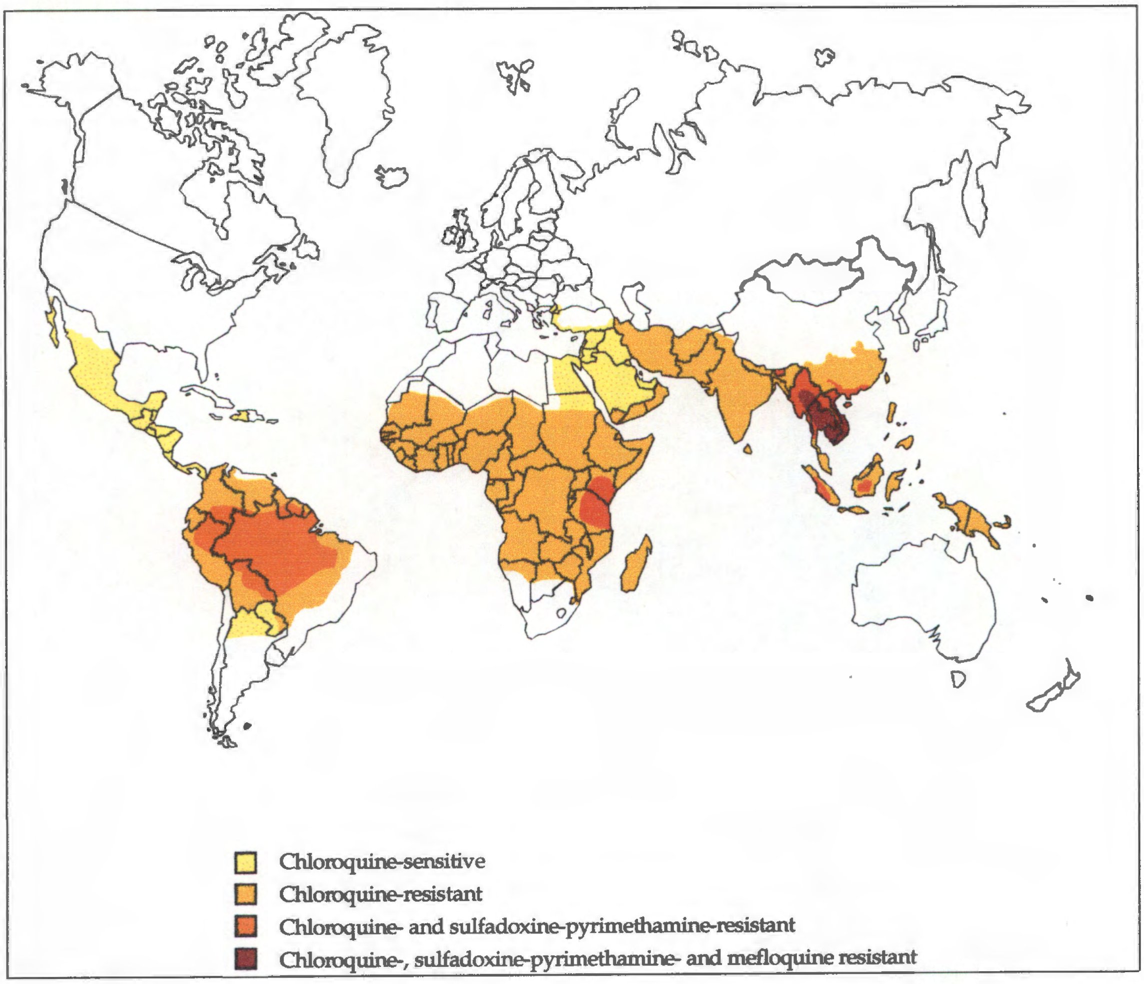


Figure 1.4. Global distribution of malaria and *P. falciparum* drug resistance in 1996 (South African Department of Health, October 1996).

The border districts generally record the highest levels of transmission, suggesting that a large proportion of South Africa's malaria problem is imported from holo-endemic areas in Mozambique, Zimbabwe and Botswana, where malaria control efforts are hampered by lack of funds and more pressing health problems. In these areas transmission occurs throughout the year. The populations in these regions tend to be semi-immune. This is not the case in South Africa, where infection is seasonal, occurring during the warm, wet months between October and April when conditions for vector breeding are optimal. This leads to a greater number of severe and complicated malaria cases and deaths, since the effects of the disease on a non-immune population are more dramatic (Sharp & le Sueur, 1996).

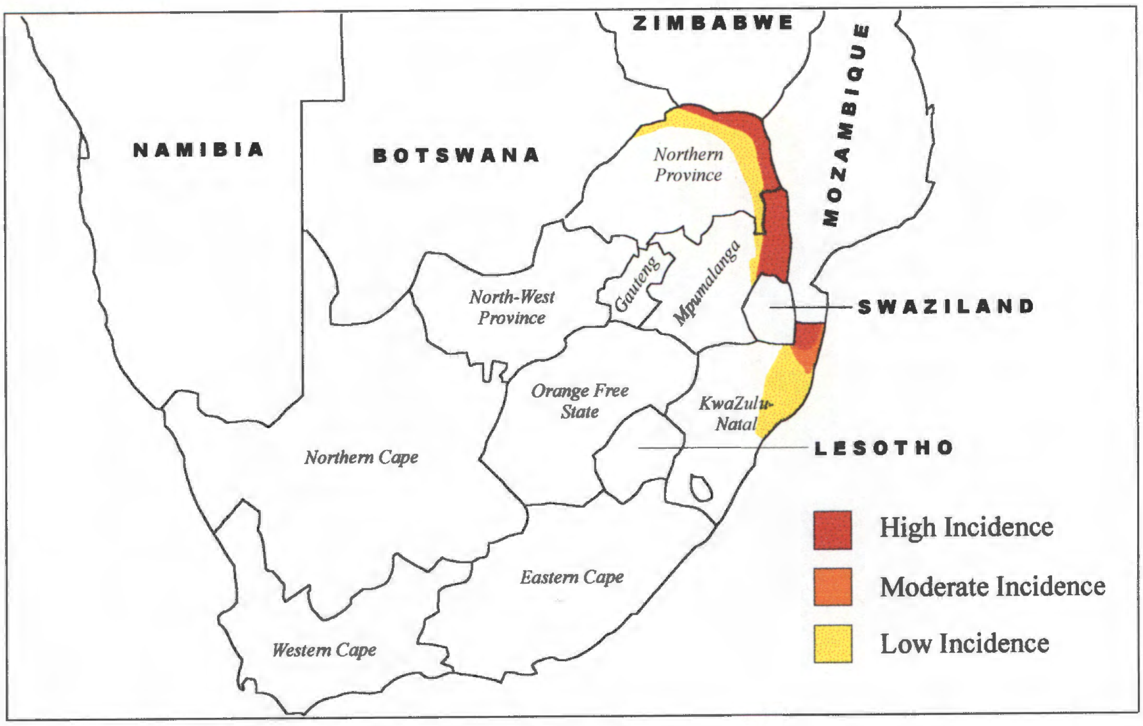


Figure 1.5. Malaria transmission zones within the borders of South Africa. Illustration courtesy of the South African Medical Research Council, with permission.

1.4. Antimalarial Drugs and Developing Resistance

Resistance to chloroquine, the drug used almost universally to treat malaria until quite recently, appeared in Africa in 1979, a short time after it emerged in Southeast Asia and South America (Fogh *et al*, 1979), and spread to South Africa by 1980 (Bac *et al*, 1985).

The relatively small number of drugs presently available for the treatment of malaria have almost entirely evolved from armed conflicts involving wealthy nations that have occurred in tropical, malaria-endemic areas. The nations perennially affected by the disease do not possess the resources to develop drugs on their own (White, 1992).

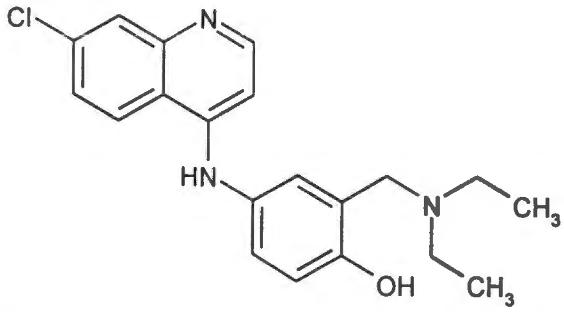
Plasmodium falciparum malaria has shown considerable ability to develop resistance to almost all the drugs with which it has been confronted over relatively short periods of time.

For the drugs discussed below, *in vivo* efficacy figures have been used wherever possible. However, where data on *in vivo* response has not been readily available, *in vitro* figures have been used. It should be pointed out that there is no correlation between *in vivo* and *in vitro* results except at high levels of resistance, perhaps due to interference in the relationship between the two tests by the immune system (ref?).

1.4.1. 4-Aminoquinolines

These are rapidly-acting blood schizontocides with some gametocytocidal activity.

1.4.1.1 Amodiaquine

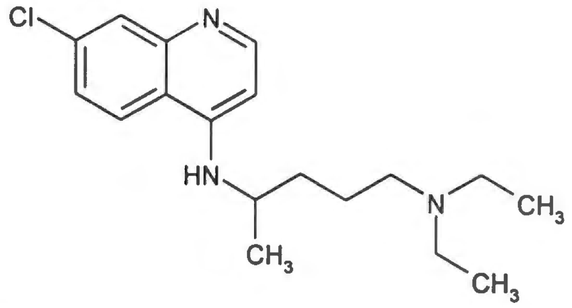


Amodiaquine, a chloroquine analogue, has a nearly-identical resistance profile to that of chloroquine, suggesting a high degree of cross-resistance. It is slightly more effective than chloroquine against chloroquine-resistant strains of the parasite (White, 1992). In southern Africa, the majority of field isolates collected were resistant to the drug by 1990 (Freese *et al*, 1994). In contrast, evidence from Gabon (Radloff *et al*, 1996) showed a cure rate of 71.83% using the drug, and a Cameroonian study (Ringwald *et al*, 1998) claimed a 100% cure rate. The latter study, however, did not quote patient numbers and ensured all patients were treated by weight, an ideal situation rarely found in the field. A review conducted by Olliaro *et al* in 1996 found that the parasitological success rate (to day 14) of amodiaquine across 24 controlled trials, 22 in Africa, was 85.44% (657 of 769 patients). However, in 1986 *P. falciparum* isolates originating in Maputo, Mozambique, sensitivity was only 24%, contrasting with the 85% found in Zambia (Freese *et al*, 1994).

The usefulness of amodiaquine is further limited by the concomitant risk of immune-mediated agranulocytosis (1 in 22000 travellers using the drug prophylactically), sometimes in association with hepatitis (1 in 15650 travellers). The drug causes a fatal reaction in 1 in 15500 travellers (White, 1996). It is no longer in use in the United States or the European Union, but is still available in parts of Africa and Oceania. Recent evidence suggests that large doses and several weeks of treatment are required to produce onset of an adverse reaction, indicating a possible application in short, intensive treatment of chloroquine-resistant *P. falciparum* malaria (Olliaro *et al*, 1996; Tester-Dalderup, 1996).

The WHO does not recommend it for treatment or prophylaxis. Amodiaquine was marketed as Camoquin in South Africa by Sterling-Winthrop until it was withdrawn from the market between 25 and 30 years ago.

1.4.1.2 *Chloroquine*



Chloroquine—4-aminoquinolone—is rapidly absorbed from the digestive tract, achieving peak serum levels in 1-6 hours. Its half-life has not been effectively determined, but is thought to range between 7-10 days and as long as 56 days. In doses recommended for prophylaxis and treatment, side effects are rare, and are generally confined to skin rashes and pruritus. Overdosing, a danger because of increasing parasite resistance to the drug, can lead to toxicity and occasionally death, especially in infants (Tester-Dalderup, 1996).

Chloroquine, once the most effective and best-tolerated antimalarial drug on the market, first exhibited resistance in the late 1950s; by the mid-1980s, resistance had spread throughout the world's malaria-endemic regions. The areas most seriously affected are sub-Saharan Africa and Southeast Asia. However, exceptions exist: resistance levels in Central America, Haiti and sections of West Africa are still relatively low. Spread of resistance in tropical regions appears to have occurred quickly, especially in Thailand. Poor malaria control policy and enormous drug pressure generated by large quantities of drug base appearing on the market, as well as subtherapeutic dosing, appear to have accelerated selection of resistant parasitic strains. Its biological half-life is typically between one and two months. Chloroquine is generally available without prescription, and is often used as a 'cure-all' for many other ailments. An example of the continuing problem is the consumption (according to the WHO) of 91 million metric tons of the drug in 1988, long after the appearance of resistance (White, 1992; Wernsdorfer, 1991). East Africa was identified as a new focus of resistance in 1977. Projections for future spread are not optimistic, based upon previous experience, and the prospects for renewed sensitivity in areas where chloroquine has been phased out, are similarly poor (Murray, 1994).

In 1993 Bloland *et al* reported that chloroquine failed to produce adequate clinical or haematological resolution in very young children suffering from *P. falciparum* malaria in Malawi and Kenya, and recommended a shift to sulfadoxine-pyrimethamine as first-line treatment in those regions.

In South Africa, resistance to chloroquine is high. Chloroquine-resistant isolates were detected by 1990 (Freese *et al*, 1994). An *in vitro* study conducted in Mpumalanga in 1996 found resistance levels approaching 80%, though this may be the result of the use of a hospital population in the study (Van Nierop & Frean, 1996). Routine data collected by the Mpumalanga Malaria Control Programme in that province between 1990 and 1995 indicate that resistance to chloroquine in the area has risen dramatically over those five years (Kruger *et al*, 1996), with a concomitant increase in both fatalities and percentage mortality (see Fig. 1.3). This association is not necessarily causally related.

Chloroquine remains effective against *P. vivax, P. ovale,* and *P. malariae,* and is still used as first-line treatment for these forms of malaria. In the former two species, treatment is immediately followed by a primaquine regimen to clear hypnozoites from the liver, thereby preventing relapse (White, 1996).

Prophylactic use entails taking a single dose weekly, starting one week before entering the area, finishing 3-4 weeks after leaving, in combination with a daily dose of proguanil. Adult dosage for chloroquine-resistant areas is 300 mg per dose (usually 2 tablets); in children, dosage is 5 mg/kg body weight. Its efficacy in Africa is approximately 72% (Bradley & Warhurst, 1995).

Other antimalarials related to chloroquine include amopyroquin, a 4-aminoquinolone related to amodiaquine, as well as piperaquine, triperaquine and dabaquine. The latter three exhibit cross-resistance with chloroquine (Tester-Dalderup, 1996).

Chloroquine is marketed in South Africa as Nivaquine by Rhône-Poulenc. Its recommended retail price in December 1997 was R15.86 per pack of fourteen 200mg tablets. It is also available at R25.14 per 100ml bottle of 50mg/5ml syrup. Tender price to the Department of Health was and is substantially lower.

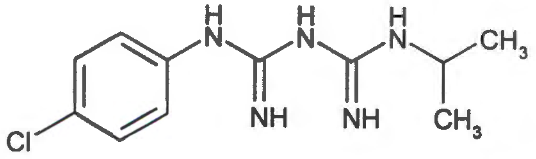
1.4.2. *8-Aminoquinolines*

These are tissue schizontocides, used primarily for preventing relapse in vivax and ovale infections. They have gametocytocidal activity as well as some activity at other points in the parasitic life cycle. Primaquine is the most commonly-used drug in this category.

1.4.3. *Biguanides*

Biguanides are dihydrofolate reductase inhibitors, tissue schizontocides and slow-acting blood schizontocides. They include proguanil and chlorproguanil, and are mainly used for prophylaxis.

1.4.3.1. *Proguanil*



Proguanil is almost exclusively used as a prophylactic drug. Standard doses are rapidly absorbed, but efficacy varies significantly between individuals. The drug is susceptible to a genetic polymorphism in one of the cytochrome P450 isoenzymes, CYP2C19, which may result in subtherapeutic plasma concentrations of its active metabolite, cycloguanil, in plasma.

Incidence of the polymorphism varies along ethnic lines (3-10% in Caucasians and up to 23% in Asians). However, *in vitro* evidence suggests that the metabolic polymorphism does not affect the effectiveness of the drug in combination with atovaquone (Edstein *et al*, 1996; see section 1.5.2).

Side effects are usually mild, and may include cutaneous rash, hair loss, mouth ulcers, abdominal discomfort and vomiting. Proguanil marketed as Paludrine in South Africa by Zeneca at R49.09 per hundred 100mg tablets (December 1997). Proguanil has been used in combination with atovaquone (see Section 1.5.2).

When used as prophylaxis, proguanil is taken daily in combination with a weekly dose of chloroquine. The effectiveness of this regimen in Africa is roughly 72% (Chanterie, 1997).

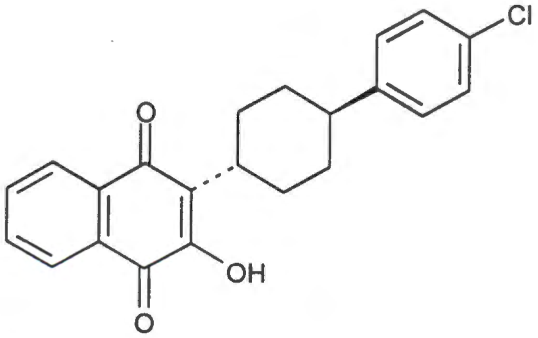
1.4.4. *Diaminopyrinamides*

Diaminopyrinamides are dihydrofolate reductase inhibitors, tissue schizontocides and slow-acting blood schizontocides. They have some sporontocidal activity, and are commonly used in combination with other antimalarials that inhibit other stages of folate synthesis; an example is sulfadoxine-pyrimethamine (see section 1.4.13).

1.4.5. *Hydroxynaphthoquinones*

This drug class is primarily used for its blood schizontocidal activity. It has also proved useful as an antiprotozoal.

1.4.5.1. *Atovaquone*



During World War II, quinine supplies were depleted faster than they could be replenished, and a replacement antimalarial was sought. This early work focussed on the hydroxynaphothoquinolones, and achieved little success. However, technological advances made since then allowed Wellcome Research Laboratories to continue the work in the 1980's, culminating in the development of atovaquone (Hudson, 1993).

Atovaquone has recently been used in the treatment of acute *P. falciparum* malaria (Looareesuwan *et al*, 1996). Results showed good antimalarial activity, but recrudescence was quite common. Research is presently underway to evaluate its effectiveness in combination with other drugs, such as proguanil and the tetracyclines, but at this time, the information is inconclusive (Looareesuwan *et al*, 1996).

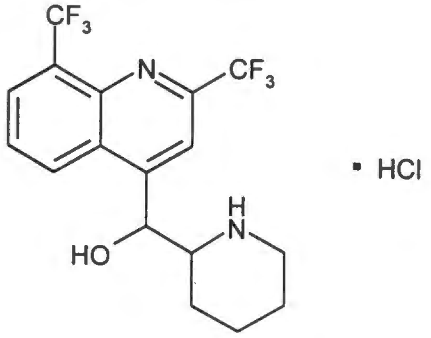
A 1996 study conducted by Radloff *et al* in Gabon found that a combination of atovaquone (1000 mg daily) and proguanil (400 mg daily) administered over 3 days to patients suffering from acute uncomplicated *P. falciparum* malaria resulted in an 87.32% cure rate, with only one recrudescence. This was significant compared with the 72% found in the control group, treated with amodiaquine. A study in Peixoto de Azevedo in Brazil (de Alencar *et al*, 1997) also showed encouraging results (76 of 77 patients cured, a 98.7% cure rate), but extrapolation from South America to sub-Saharan Africa is not possible. Glaxo Wellcome recently made a donation of one million doses per year of the atovaquone-proguanil combination (Malarone) to malaria-endemic areas in Africa, Southeast Asia, and South America, although reaction to this has been mixed. There has been debate over its impact on developing resistance, and whether a new non-essential antimalarial will do more harm than good for the continent. Atovaquone resistance stems from a single point mutation, suggesting the usefulness of the Malarone combination may be short-lived (Bloland *et al*, 1997; Phillips-Howard, 1998).

In South Africa Glaxo Wellcome markets atovaquone alone as Wellvone. Its December 1997 recommended retail price was R2348.86 per one hundred and eighty-nine 250mg tablets. Malarone's international price was recently fixed at UK £21.00 per adult course.

1.4.6. 4-Methanolquinolines

4-Methanolquinolines are rapid-acting blood schizontocides with some gametocytocidal activity.

1.4.6.1. Mefloquine



Mefloquine, a highly active quinoline-methanol schizontocide, was developed by the U.S. Army's antimalarial research programme. Absorption is rapid and serum peak levels occur in 1-4 hours. Half-life is extremely variable, falling between 7 and 30 days. Single, high doses produce good cure rates, and use of the drug for prophylaxis is common. However, epidemiological evidence has shown that therapeutic doses may produce mild side effects, including nausea, diarrhoea, abdominal pain, dizziness, vivid dreams, and insomnia. More rarely, severe neuropsychiatric derangement may occur, though the incidence of this is unclear (Tester-Dalderup, 1996). Mefloquine exhibits serious cardiac interactions with quinine, quinidine, chloroquine, and especially halofantrine (DRUGDEX®, 1998; World Health Organisation, 1998).

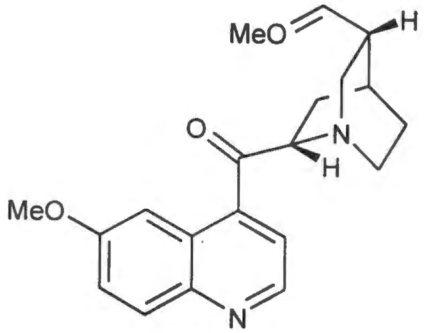
Initial studies of mefloquine indicated high efficacy, but these results may have been optimistic. Resistance in Southeast Asia has increased dramatically since it was introduced as first-line agent in Thailand in late 1984. Intrinsic resistance was reported in West Africa in 1988, but in most other parts of the world, it remains a viable alternative therapy. There are, however, fears that resistance to mefloquine may in turn stimulate resistance to quinine, the only agent available for the treatment of severe and complicated malaria (White, 1992; Wernsdorfer, 1991). Mefloquine resistance in southern Africa had not appeared by 1994, though sample sizes used in the assessment of *in vitro* isolate sensitivity were small (Freese *et al*, 1994; Deacon *et al*, 1994).

When used prophylactically, weekly doses of 250 mg (1 tablet) are indicated in adults. In children, dosage should be 5 mg/kg body weight per week. Prophylactic use should start one week before entering the area and end four weeks after leaving. Effectiveness as prophylaxis in East Africa has been reported to be 91% (Steffen *et al*, 1993), while another study, using a smaller study population, reports a prophylactic failure rate of 33% (5 of 15 subjects) (Lobel *et al*, 1998). A Nigerian study revealed a cure rate of 93.9% (31 of 33) in children with multi-drug resistant *P. falciparum* malaria (Okoyeh *et al*, 1997). Studies conducted in Burkina Faso indicated full sensitivity to mefloquine (Del Nero *et al*, 1993; Del Nero *et al*, 1994).

WHO recommendations for treatment are 15 mg/kg (up to 1 000mg) as a single dose. However, current practice is to give 25 mg/kg over 2-3 days, up to 1 500 mg (personal communication, K I Barnes). Mefloquine is not currently registered for treatment in South Africa.

Mefloquine is available in South Africa by Roche as Lariam,. at a recommended retail price of R128.66 per pack of eight 250mg tablets, for malaria prophylaxis.

1.4.6.2. Quinine



Oral quinine is well absorbed and has an elimination half-life of 11 hours. Plasma concentrations above the minimum inhibitory concentration must be maintained for the drug to be effective. Adverse effects occur commonly in overdose, or too-rapid intravenous treatment. These include central nervous system disorders, visual disorders, and cardiovascular problems (Tester-Dalderup, 1996).

Quinine, generally used in combination with tetracycline, has mainly retained its efficacy in most parts of the world (with the exception of Southeast Asia) in the 350 years since its discovery in Peru in the early 17th century. Meshnick has proposed that this may be due to a unique, specific mode of action in the parasite that is resistant to mutation, or because development of resistance has been so slow that it has not been noticed. A final possible explanation may be that its level of use has not been sufficient to produce enough drug pressure (Meshnick, 1997). Notable exceptions are Thailand and parts of Africa. Quinine, however, is not as useful a first-line agent as some other drugs due to its serious side effects in up to 70% of patients and concomitant low compliance rate (White, 1996; Luzzi & Peta, 1993). This, paradoxically, may also explain its low resistance levels. It is still, however, widely used in the treatment of severe and complicated malaria (White, 1992; Wernsdorfer, 1991).

Quinine combinations are used as first-line treatment in urban non-malaria-endemic areas of South Africa, as well as in industrialised Western nations. It is not used as first-line therapy in rural areas because of its strict dosage regimen and side effects. Short-course quinine therapy combined with a single dose of sulfadoxine-pyrimethamine has been found to be effective in Kenya (Keuter *et al*, 1992) and Brazil (de Souza *et al*, 1985). Current South African recommendations support a full 7-day quinine regimen in combination with the standard single dose of sulfadoxine-pyrimethamine (South African Department of Health, 1996). Quinine is also used in combination with doxycycline (see section 1.4.4).

African strains of *P. falciparum* are reportedly more sensitive to quinine than those originating in Southeast Asia and South America. *In vivo* studies conducted in Africa since 1980 have shown quinine sensitivity in virtually all cases (Salako, 1985; Freese *et al*, 1994).

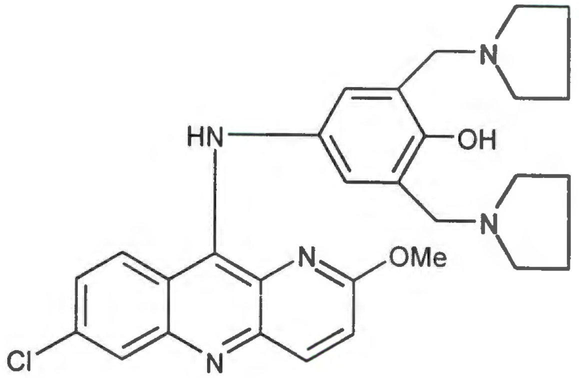
Intravenous quinine is generally administered, although quinidine is often substituted in the United States of America. Injectable quinine in lactate form is available as quinoform. Few data are available on the latter's side effect profile, but efficacy is identical to quinine (Tester-Dalderup, 1996).

The oral formulation is marketed in South Africa by Lennon, as Lennon-Quinine Sulphate. Intravenous (Adco-Quinine) formulations are marketed by Adcock-Ingram. Cost in December 1997 was R145.92 per pack of one hundred 300mg tablets and R115.65 per ten 1ml ampoules (containing 300mg).

1.4.7. *Naphthyridine derivatives*

Not much is known about this class of antimalarial. Its most prominent member is pyronaridine.

1.4.7.1. *Pyronaridine*



Developed in China in the early 1970's, the azacridine-derived drug pyronaridine has shown promise in the treatment of uncomplicated *P. falciparum* malaria in Southeast Asia. This and other research has also shown that it may be useful in chloroquine-resistant areas (Ringwald *et al*, 1996; WHO, 1996). The Ringwald study, conducted in Yaoundé, Cameroon, found a 100% parasite clearance rate in patients treated with 32 mg/kg pyronaridine within 14 days, compared with 44% in chloroquine. Parasitaemia in the pyronaridine group (40 of 81) was cleared by day 4. Two further studies at Yaoundé found 100% efficacy for *P. malariae* and *P. ovale* infections (Ringwald et al, 1997) and a 100% efficacy rate in falciparum-infected paediatric patients (41 of 41) in comparison with 60% (16 of 40) with chloroquine (Ringwald *et al*, 1998).

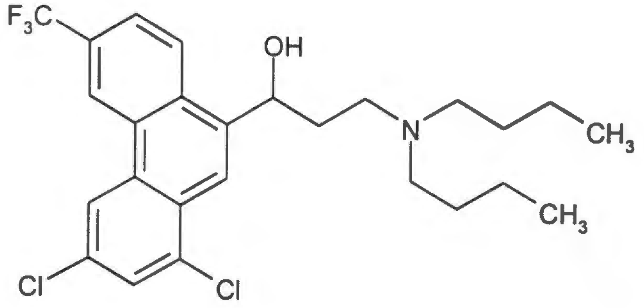
Resistance of *P. falciparum* to pyronaridine in Africa has not been reported. A Thai study reported a 63% cure rate (38 of 60 subjects) after 28 days when treated with 1 200mg over 3 days, and an 88% cure rate (23 of 32) after 28 days when using a regimen of 1 800mg over 5 days (Looareesuwan *et al*, 1996).

Dose schedules are empirical and little is known about the drug's pharmacokinetics. Furthermore, resistance is easily induced *in vitro*, and at a 1996 cost of roughly $3.00 per adult dose, it may prove to be an expensive alternative (Winstanley, 1996).

1.4.8. 9-Phenanthrenemethanols

These are blood schizontocides.

1.4.8.1. *Halofantrine*



Halofantrine is a phenanthrine-methanol compound, and is relatively slowly absorbed, with peak serum levels occurring within 3.5-6 hours. Side effects from normal dosages are mild, and include nausea, diarrhoea, headache and pruritus. Standard doses may produce severe cardiac effects. Its use with mefloquine is strongly contraindicated, due to the risk of serious cardiac-related interaction (Tester-Dalderup, 1996; Nosten *et al*, 1993). Falade et al found an *in vivo* resistance level of 17.95% in Nigeria in 1998, which corresponds well to the 18% found in Brazzaville, Congo (Brasseur *et al*, 1993). Brasseur *et al* also noted a rapid onset of resistance, thought to be due to high drug pressure in the region. However, a study conducted in Lambaréné, Gabon found a 100% cure rate (35 of 35 adult patients with uncomplicated falciparum malaria) when comparing 8 mg/kg halofantrine, given 6-hourly for 3 doses, with chloroquine-antibiotic combinations (Kremsner *et al*, 1994). Another study, evaluating malaria-infected nonimmune travellers returning to Europe from sub-Saharan Africa, found a 14.29% recrudescence rate (4 of 28 patients) with halofantrine treatment (250mg 6-hourly for 3 doses). Of the 4 recrudescences, poor absorption of the drug was responsible for two and *in vitro* resistance was found in isolates from the other two (Bouchaud *et al*, 1994).

Halofantrine is only of use in treating mild-to-moderate uncomplicated malaria. Due to its poor and highly variable bioavailability, standard doses may be subtherapeutic in some individuals and toxic in others (White, 1996; ter Kuile *et al*, 1993). This interindividual variability has led to the adoption of a micronized formulation for some studies. An adult treatment course is six 250mg tablets, 2 tablets every 6 hours. If no cure occurs, the course is to be repeated one week afterward (Halfan package insert).

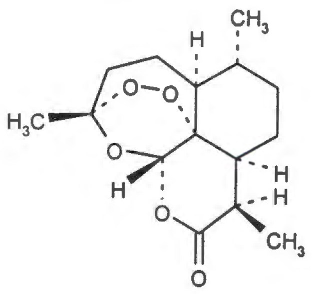
SmithKline Beecham markets the drug in South Africa as Halfan, and its December 1997 recommended retail price was R39.79 per six 250mg tablets, or one adult treatment course.

Other endoperoxide antimalarials in use include pefloxin, a fluoroquinolone antibiotic which has been shown to inhibit *P. falciparum in vitro*, and pentoxifylline, a methylxanthine which may prevent the onset of cerebral malaria (Tester-Dalderup, 1996).

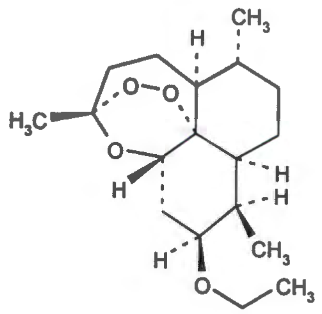
1.4.9. *Sesquiterpene lactones*

These compounds have blood schizontocidal activity, and consist chiefly of the artemisinin derivatives.

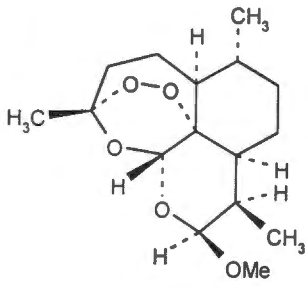
1.4.9.1. *Artemisinin derivatives*



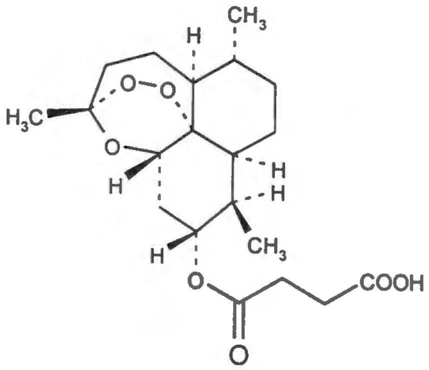
Artemisinin



Arteether



Artemether



Artesunate

The artemisinin derivatives arose from an ancient Chinese remedy for fever, the herb Qinghaosu (*Artemisia annua* L). Chinese researchers extracted the herb's active principle, a sesquiterpene lactone peroxide which they named artemisinin. As well as artemisinin, three semi-synthetic preparations exist, based upon the compound dihydroartemisinin (DHA). At the time of writing (early 1999), artemisinin is subject to stringent World Health Organisation guidelines designed to prevent the development of resistance. According to these, artemisinin may only be used in treatment (not prophylaxis), and then only in multi-drug resistant malaria not responding to quinine treatment; may only be used in combination with mefloquine; and must be used for at least 3 days. At present, artemisinin is only available in South Africa on a named-patient basis, subject to clearance from the Department of Health (White, 1996; WHO, 1993).

There is evidence that artemisinin compounds may already be in significant use in Africa, in disregard of WHO guidelines, which may compromise their future usefulness on the continent.

Arteether is the ether ethyl derivative of DHA, and had been selected for further development by the WHO, but is no longer being pursued. Its Chinese discoverers have abandoned it as it is reportedly more toxic than the other derivatives. Artemether is the methyl ether derivative of DHA. Its action is thought to be faster than that of the other two primary derivatives, and has been used successfully in the treatment of both severe and complicated malaria.

Artesunate is a water-soluble hemisuccinate variant of DHA. A 3-day course in combination with mefloquine has been shown to be effective against multidrug-resistant *P. falciparum.* (White, 1996; Nosten & Price, 1995). However, strains of *P. falciparum* resistant to mefloquine have been noted to be less sensitive to artemisinin, perhaps due to the synergistic relationship between the two drugs (WHO, 1998).

The World Health Organisation has recommended that the 3-day course with mefloquine be adopted preferentially due to the high recrudescence rate found in short-course monotherapy, the problem of compliance in longer-duration monotherapy, and to delay the emergence of resistance (WHO, 1998).

All three derivatives are rapidly metabolised to the biologically active form of the drug, DHA. Clinical and parasitological response is faster than with other antimalarials, and little resistance has as yet been reported. Its mode of action is not clear at this time. Animal testing suggests that there is a significant risk of neurotoxicity, but little evidence has appeared in human subjects (Nosten & Price, 1995; Hoffman, 1996).

Resistance to the artemisinin derivatives is rare in Southeast Asia, and has been reported in one West African isolate (Gay *et al*, 1994). Treatment failures have been reported in Thailand (Luxemburger et *al*, 1998).

Artesunate is produced in Vietnam at US$ 1.00 per twelve 250mg tablets, but in Thailand, where it is also a first-line antimalarial, twelve 250mg tablets cost US$ 3.60. South African prices may not be similar to Thai prices when the drug is introduced.

1.4.10. Sulphonamides

Sulphonamides inhibit dihydropteroate and folate synthesis, and have blood schizontocidal activity. They are generally given in combination with pyrimethamine (see section 1.4.13).

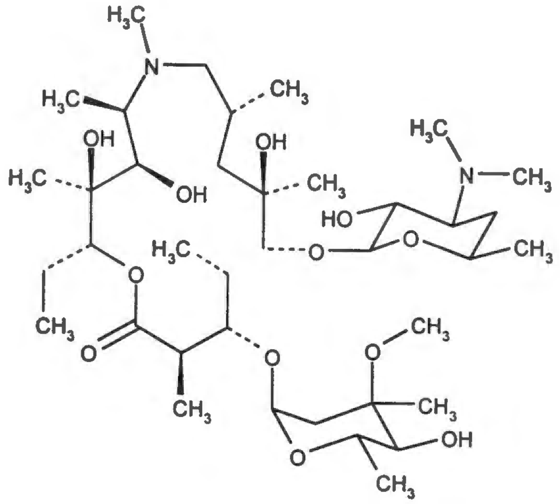
1.4.11. Sulphones

Sulphones are folate synthesis inhibitors with a blood schizontocidal action. They are often given in combination with pyrimethamine or chlorproguanil (see section 1.4.13).

1.4.12. *Antibiotics*

The tetracyclines are the principal drugs in this category, and have blood and some tissue schizontocidal activity.

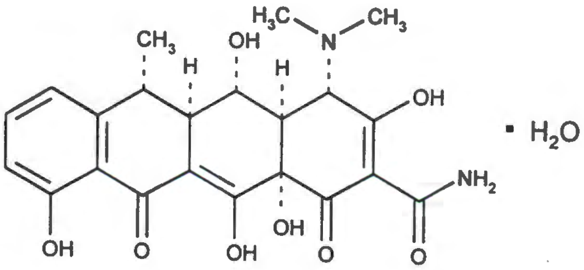
1.4.12.1. *Azithromycin*



Azithromycin, an azalide antibiotic, is presently under consideration for the treatment and prophylaxis of malaria. It is reportedly effective in parasite clearance, but its value in prophylaxis is controversial. Evidence currently does not support its use as an antimalarial agent (Sadiq *et al*, 1995).

Pfizer have made the drug commercially available in South Africa as Zithromax. In December 1997, its recommended retail price was R80.32 for three 500mg tablets.

1.4.12.2. *Doxycycline*



Although generally used as an antibacterial agent, the tetracycline antibiotic doxycycline is often used as prophylaxis against *Plasmodium* infections. Its side effect profile is markedly different from most other antimalarials, including skin photosensitivity, gastrointestinal upset, and Candida superinfection of the gut and vagina (Chanterie, 1997).

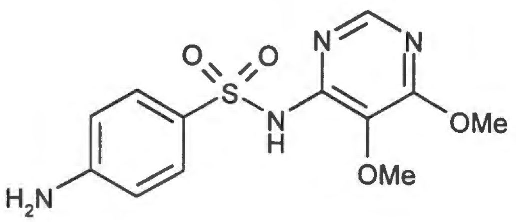
In combination with quinine, a 7-day treatment regimen is generally effective in 85% of cases, but compliance is poor due to quinine's cinchonistic side effects (Smith *et al*, 1997).

Doxycycline is indicated in individuals visiting high-risk areas that are unable to use other prophylactic agents, as well as travellers to regions of high mefloquine resistance. Dosage of 100 mg per day should begin 1-2 days before entering the area, and end four weeks after departure. Dosage in children over 8 years of age is 2 mg/kg body weight, not exceeding 100 mg per day. Doxycycline cannot be used for longer than 4 months without medical advice, and is contraindicated in pregnancy and in children younger than 8 years (Chanterie *et al*, 1997).

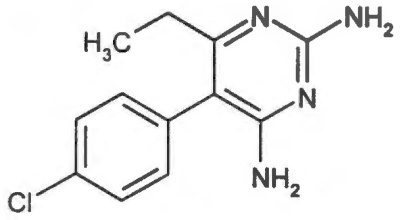
In South Africa, doxycycline is available as Doxycyl from Lennon Meds at a December 1997 recommended retail price of R159.54 per hundred 100mg capsules.

1.4.13. *Combinations*

1.4.13.1. *Sulfadoxine-pyrimethamine ('Fansidar')*



Sulfadoxine



Pyrimethamine

The sulfadoxine-pyrimethamine combination was introduced as first-line therapy in KwaZulu-Natal in 1990, replacing chloroquine, and has proved effective (Freese *et al*, in press).

Pyrimethamine is the most active of the 2-4-diaminopyrimidines against malaria-causing plasmodia, and is well absorbed, reaching peak plasma levels in 2-6 hours. Its half-life is in the order of 80-95 hours, and its effectiveness is enhanced when used in combination with a sulfonamide antibiotic, as in the formulation of Fansidar (25 mg pyrimethamine + 500 mg sulfadoxine).

Sulfadoxine-pyrimethamine treatment is associated with a considerable number of side effects. Haematological symptoms including leukopenia, agranulocytosis, thrombocytopenia and pancytopenia occur occasionally during treatment for malaria, as well as severe cutaneous adverse reactions. The high frequency of adverse event prevents its use as a prophylactic drug (Tester-Dalderup, 1996). A review conducted by Roche (Stürchler *et al*, 1993) claimed that the frequency of severe cutaneous adverse reactions was 0.1 per million in developing countries, where the drug was administered as a single dose.

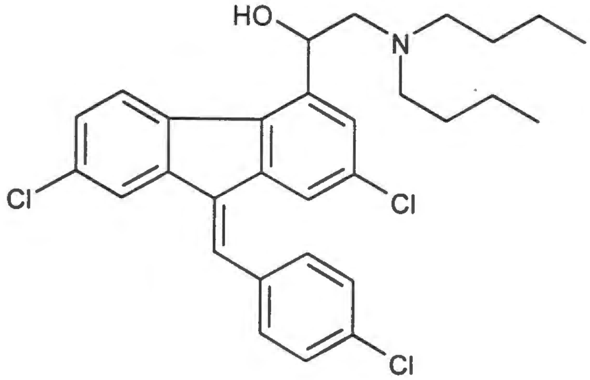
The sulfadoxine-pyrimethamine therapy option has come to the fore in areas severely affected by chloroquine resistance, where it is somewhat more effective (White, 1992). However, substantial resistance in *P. falciparum* has developed in Southeast Asia, Central America and parts of tropical Africa, such that its usefulness is becoming increasingly limited. The drug is, however, well-tolerated, and may be given in a single dose, making it a useful first-line therapy (White, 1992; Wernsdorfer, 1991). It has been used in KwaZulu-Natal since January 1988; 1990 isolates showed reduced parasite sensitivity to the drug in the area (Freese *et al*, 1994). The drug was introduced recently as first-line treatment in Mpumalanga Province.

Some problems have emerged in the sub-Saharan African milieu recently. Paediatric dosage inconsistencies were recently detected in Kenya, where age-specific differences in routine prescription practice resulted in subtherapeutic drug levels in some age groups. The switch from chloroquine's 3-day regimen to a single dose has created suspicion regarding sulfadoxine-pyrimethamine efficacy among patients, resulting in increased self-medication. This problem is further complicated by sulfadoxine-pyrimethamine's seeming 'delay in effect' stemming from its stage-specificity, and it's lack of significant antipyretic and anti-inflammatory effect. Repeat prescription has been found to be common in Kenya (Phillips-Howard, 1998).

Fansidar is made available in South Africa by Roche at R34.13 per pack of 3 tablets (December 1997). Tender price to the Department of Health was somewhat lower, at about R18.50 per adult course.

Other combination therapies using pyrimethamine include 'Maloprim' (12.5 mg pyrimethamine + 100 mg dapsone), 'Deltaprim' (25 mg pyrimethamine + 100 mg dapsone), 'Fansimef' (25 mg pyrimethamine + 500 mg sulfadoxine + 250 mg mefloquine), pyrimethamine-trimethoprim, pyrimethamine-clindamycin, and pyrimethamine-clarithromycin (Tester-Dalderup, 1996).

1.4.13.2. *Artemether-benflumetol ('Co-artemether')*



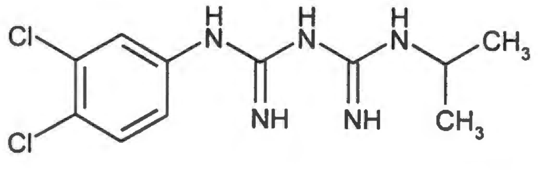
Benflumetol (lumefantrine) is a new antimalarial originating in China. It is presently being developed by Novartis as CGP 56697, in combination with artemether. The combination is commonly known as co-artemether. Several *in vitro* clinical trials testing its efficacy have been conducted.

In Thailand, co-artemether was compared with artesunate-mefloquine in 617 acute patients with multidrug-resistant falciparum malaria; there was no difference in initial therapeutic response, but cure rate was significantly different at day 63 (81% in co-artemether vs. 94% in artesunate-mefloquine, $P<0.001$) (van Vugt *et al*, 1998). A Gambian study in 287 children found co-artemether to be 100% effective in clearing gametocytes when compared with sulfadoxine-pyrimethamine (71.1%, $P<0.0001$). However, the day 15 cure rate was better in sulfadoxine-pyrimethamine (97.7%) than in co-artemether (93.3%, $P<0.003$) (von Seidlein *et al*, 1998). Van Vugt *et al* conducted a double-blind trial with 359 patients at Mae Sot, Thailand, comparing a six-dose regimen of artemether-benflumetol (a total dosage of 480mg artemether + 2 880mg benflumetol) to the four-day regimen used previously at the same study site. The 28-day cure rate among the 6-dose groups were 96.9% and 99.1%, while that of the 4-dose group was 83% (van Vugt *et al*, 1999).

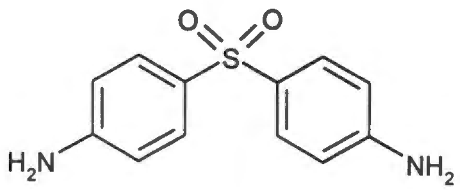
A further trial in Kilombero, Tanzania, found an overall parasitological cure rate of 86.4% in 260 children, in comparison to 10.3% with the chloroquine group (Hatz *et al*, 1998). An *in vitro* study investigating the susceptibility of 158 Senegalese *P. falciparum* isolates to benflumetol found reduced efficacy in 6% of patients. No cross-resistance was detected (Pradines, 1999).

Novartis will market co-artemether in South Africa as Riamet. It will be composed of 20mg artemether in combination with 120mg benflumetol. So far, the combination has only been registered in Switzerland, where it is available at 58.80 SFr for 16 tablets, and 78.75 SFr for 24 (personal communication, C Ford, Novartis South Africa).

1.4.13.3. *Chlorproguanil-dapsone ('LapDap')*



Chlorproguanil



Dapsone

LapDap, as it is known, represents a potential 'salvage therapy' in the case of sulfadoxine-pyrimethamine failure. Its short half-life and antifolate mode of action make it a viable alternative.

A trial of chlorproguanil-dapsone efficacy was conducted by Keuter *et al* in Kakamega, Kenya, in 1990. It concluded that the combination was effective in clearing parasitemia by day 7 in comparison with chloroquine and sulfadoxine-pyrimethamine, but also found a 67% recrudescence rate by day 28. Another study was conducted by Amukoye *et al* in Kilifi, Kenya, in 1997. It showed that a three-dose regimen was effective in the treatment of *P. falciparum* malaria, although not as effective as sulfadoxine-pyrimethamine (SP). The authors concluded that chlorproguanil-dapsone should be developed in order to slow the emergence of antifolate resistance in Africa, as well as for a salvage role in the event of SP treatment failure.

The dosage used in both studies was 1.2 mg/kg chlorproguanil and 2.4 mg/kg dapsone per dose. However, final recommended dosages for LapDap have not been finalised.

1.5. Summary of First-Line Antimalarial Treatments

Agent	Resistance in Sub-Saharan Africa	Cost per Adult Course	Analysis
Amodiaquine	Moderate	R12.57	Subject of renewed interest, but moderate resistance levels. Cross resistant with chloroquine.
Artesunate	Low to Absent	R8.06[*]	Effective, but subject to stringent WHO guidelines for prevention of resistance
Atovaquone/ Proguanil	Low	R168.00	Results to date inconclusive
Chloroquine	Very High	R0.99	Ineffective
Halofantrine	Low to Moderate	R79.58	Risk of serious cardiac complications, poor bioavailability
Mefloquine	Low to Moderate	R96.50[**]	Risk of adverse events, risk of encouraging quinine resistance
Pyronaridine	Low to Absent	R9.02[***]	Effective
Quinine (O)	Low	R38.01	Risk of adverse events and low compliance preclude use as first-line agent
Quinine (O)/ Doxycycline	Low	R52.37	Risk of adverse events and low compliance cast doubts on use as first-line treatment
Sulfadoxine-pyrimethamine	Moderate	R18.50	Risk of adverse events; single-dose regimen enhances compliance

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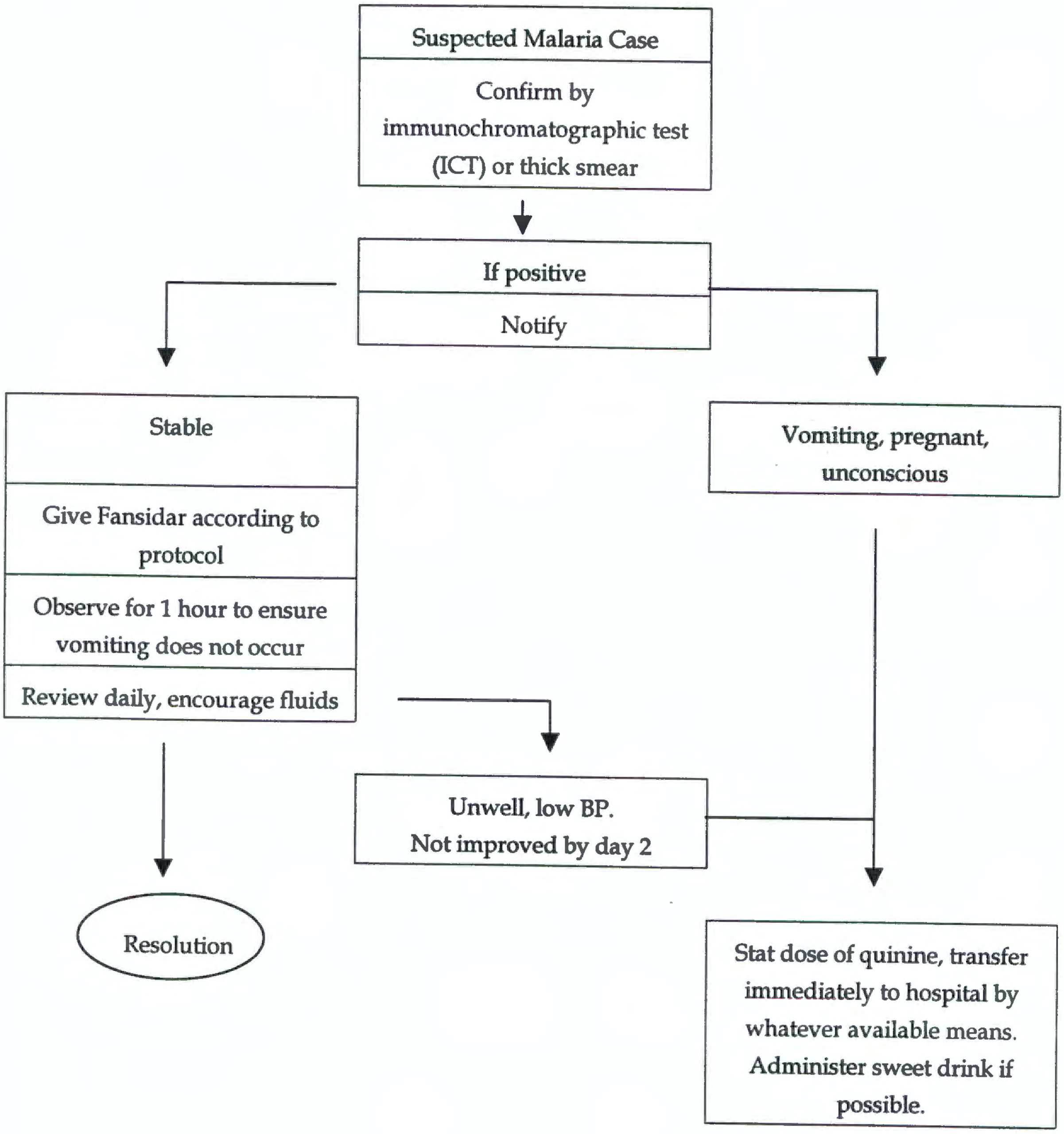
[*] Based on Thai market prices in 1997, and a mean 1997 US$/ZAR exchange rate of 4.6072.

[**] Assuming average adult weight >70kg.

[***] Based upon WHO estimates of final cost in Africa (personal communication, T Kanyok, Pyronaridine Manager, WHO).

1.6. Treatment of Malaria in the Shongwe and Tonga Districts of Mpumalanga, South Africa

The Shongwe and Tonga districts of Mpumalanga use the following malaria treatment protocol:



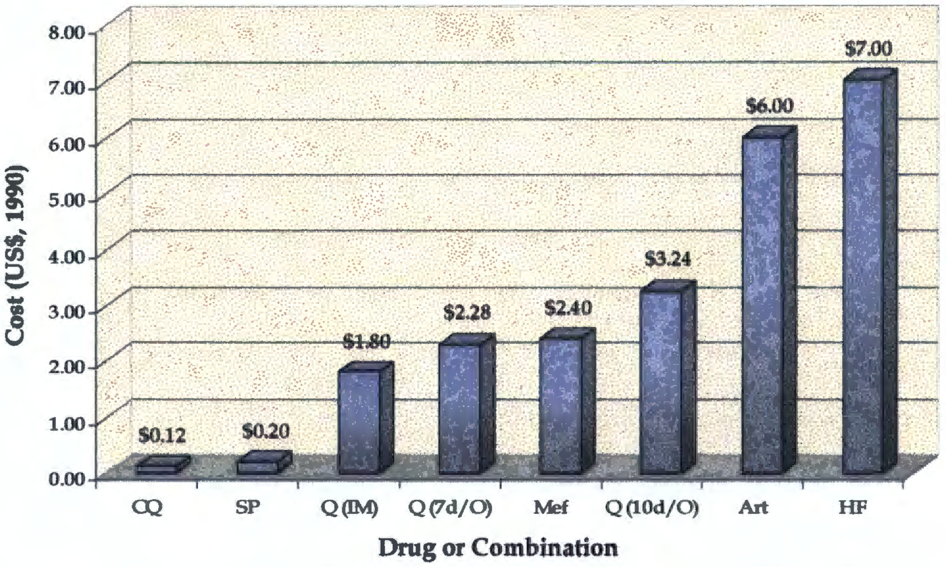


Figure 1.6. Relative costs of antimalarial drugs in 1990, based upon WHO estimates (Phillips & Phillips-Howard, 1996; Schapira et al, 1993) (CQ=chloroquine, SP=sulfadoxine-pyrimethamine, Q(IM)=intramuscular quinine, Q(7d/O)=oral quinine for 7 days, Mef=mefloquine, Q(10d/O)=oral quinine for 10 days, Art=artemisinin, HF=halofantrine.) These prices are not consistent with South African market prices.

1.7. Economic Implications of Resistance to Antimalarial Drugs

The World Bank and the World Health Organization determined that a single malaria case costs the equivalent of 10 working days in Africa (World Bank, 1993). If this figure is multiplied by a million cases (in working adults between the ages of 18 and 45) a year, the result is about 10 million working days lost per annum (Murray, 1994). Added to this, drug treatment costs between US$ 0.08 and US$ 5.30 per case depending on the drug used, which is in turn dependent on the resistance profile of the parasite. Since resistance is becoming more widespread, drug costs are rising proportionately. The projected cost of malaria in Sub-Saharan Africa in 1995 was US$ 1 800-million (Murray, 1994; Velásquez & Boulet, 1997).

Chloroquine was the drug of choice for the treatment of *P. falciparum* malaria until the mid-Eighties. It was inexpensive (US$ 0.12 per treatment course, 1990) and widely available. However, once resistance emerged it became clear that cost-effective alternatives were needed. The first of these to be introduced was sulfadoxine-pyrimethamine, which was introduced at a cost of US$ 0.20 per treatment course, or 1.67 times the cost of its predecessor. However, the appearance of sulfadoxine-pyrimethamine resistance forced the introduction of more expensive drug therapies, mefloquine chief among them (Phillips & Phillips-Howard, 1996).

Poorer malaria-endemic nations faced with the problem of rapidly-increasing drug resistance are ill-equipped to make the switch to more effective therapy, often suffering from already-strained health budgets. According to a WHO survey in 1990, the switch from chloroquine to sulfadoxine-pyrimethamine may increase first-line drug costs by between 67% and 1800%, depending on the country and the source of the import (Phillips & Phillips-Howard, 1996; Schapira, 1993). South Africa was, until recently, in the unique position in Africa of having to purchase sulfadoxine-pyrimethamine ('Fansidar') from Switzerland at the price charged to developed Western customers, while other sub-Saharan nations are able to obtain the drug from France at substantially-discounted prices. This remains the case for several other patented antimalarials.

The switch from sulfadoxine-pyrimethamine to mefloquine would lead to an elevenfold increase in drug costs; changing from mefloquine to artemisinin would increase drug costs by a further 150%, a total increase of more than 5700% over the cost of chloroquine treatment.

Another problem area is compliance. Sulfadoxine-pyrimethamine is convenient in this regard, since it is administered in a single dose, and the patient can be monitored by nursing or clinic staff to ensure that the drug is not vomited up before it is absorbed. Chloroquine, and all other antimalarials, requires a multi-dose regimen, and it is consequently far more difficult to ensure that the drug or combination in question is correctly and effectively used.

1.8. Pharmacoeconomics

Pharmacoeconomics is a relatively new field. It is a branch of outcomes research, which is defined as research that attempts to identify, measure, and evaluate the end results of health care services. These include clinical effects, functional status, wellbeing, and satisfaction with care. This field is generally subdivided into evaluation of variations in clinical practice patterns, effectiveness of treatments and other interventions, appropriateness of therapeutic alternatives, tools for the identification of patient preferences regarding treatment options, and methods for evaluating changes in health status and patient satisfaction with health care (Bootman, 1995). The first published work in the field of pharmacoeconomics appeared in 1978.

1.8.1. *Pharmacoeconomics Methodology*

In order to qualify as full economic evaluation, all studies must satisfy two criteria: two or more alternatives must be compared, and both inputs (costs) and outcomes (consequences) must be fully investigated. The choice of one drug therapy over others must include a comparison of that therapy with the most frequently used alternatives in routine clinical practice, which might also include 'do nothing'.

In addition, any evaluation must address hidden costs associated with the drug therapies under consideration: these might include hospital stays, clinical staff time, use of consumables, and travel costs. Costs in pharmacoeconomic studies are generally divided into two types: *direct* costs, which deal with short-term expenses associated with a particular therapy, such as drug costs and salaries of health professionals, and *indirect* costs.

Indirect costs, or hidden costs, are the subject of some controversy. They have, in the past been estimated by means of the human capital method, whereby the potential value of lost production through disease is measured. Recently, Koopmanschap and Rutten pioneered the friction cost method, an alternative approach that measures the amount of production lost to disease by means of the time necessary for an affected organization to return production to initial levels (Koopmanschap & Rutten, 1996). Since then the topic has been the source of some debate (Johannesson & Karlsson, 1997; Koopmanschap *et al*, 1997).

All costs involved in drug therapy must be considered in a complete economic analysis, taking into account the resource use falling on all parties: the health system, patients, caregivers, employers, and society.

Finally, it is important to report on the evaluation of all identified costs and outcomes clearly and unequivocally. This transparency demonstrates the soundness of the approach and allows other researchers to adapt the methodology employed to other circumstances.

1.8.2. *Controversies of Outcomes Research*

Besides the disagreements over indirect costs, outcomes research and pharmacoeconomics in particular have inspired lively discussion.

Bradley *et al* reported in 1995 that, while 73% of 90 medical and health care journal articles published between January 1989 and December 1993 were rated as adequate in terms of quality, 24%-33% of publications failed to address the issue of perspective correctly. In addition, an enormous 71%-87% of papers dealt inadequately with ethics (Bootman, 1995). Perhaps more importantly, statistical aspects have been neglected in some cases (Bradley *et al*, 1995).

The prospect of cost containment taking precedence over effective treatment is disturbing. In the case of malaria, this approach to management of the disease can only lead to increased resistance, increased morbidity and mortality, and a subsequent increase in economic damage to a country that overwhelms any saving in drug or treatment costs that might have been achieved. The true value of pharmacoeconomic research is that it seeks to associate outcomes with costs and thus can indicate potential value for money.

Current opinion on standards for outcomes research is mixed, and the subject matter highly controversial. The American Food and Drug Administration (FDA), while having no official policy on pharmacoeconomic studies, has taken the position that only those studies based on 'truthful and non-misleading information' are acceptable. By implication, this includes only the results of randomized clinical trials.

1.8.3. *Cost-Effectiveness Analyses*

Reeder describes the health care system as an 'interrelationship of the budgetary (payment) and delivery system', a 'production process' in which resources such as pharmaceuticals, attention from medical professionals, inpatient hospital care, and outpatient services are combined to create a medical outcome, measured in 'natural units'. The most efficient combination of these resources to achieve an acceptable, defined patient outcome is the final goal of any pharmacoeconomic study (Reeder, 1995).

The specific method of pharmacoeconomic research used here is cost-effectiveness analysis, a technique used to compare the costs and consequences of alternative approaches to addressing a health-care issue, in this case the effective treatment of malaria (Reeder, 1995).

In cost-effectiveness analyses (CEA), costs are measured as monetary values, while outcomes are described in natural units common to all comparators. Outcomes are measured in terms of a specific therapeutic objective. A cost-effective alternative may not necessarily be a less expensive one: drug therapies are deemed to be cost-effective if one of three criteria is met:

- The cost-effective alternative is less expensive and as effective as its comparators;
- The cost-effective alternative is the same cost but more effective than its comparators; or
- The cost-effective alternative is more expensive than its comparators, but delivers a greater benefit that is deemed worth the additional cost.

CEA provides the means to identify the optimal health care outcome per monetary unit spent from a number of alternative drug therapies. Results may be expressed in one of two ways:

- The **Average Cost-Effectiveness Ratio (ACER)**: This is a measure of the average cost of obtaining a specific therapeutic outcome, spread over a large population.
- The **Incremental Cost-Effectiveness Ration (ICER)**: This approach reflects the additional cost and additional benefit gained when an optimal alternative is compared to the next-best option.

1.8.4. *Sensitivity Analysis and Discounting*

Pharmacoeconomic analyses contain an unavoidable degree of uncertainty: assumptions must often be made concerning compliance and choice of discount rate, and data invariably contains uncertainties and biases. Precision is limited by these factors, necessitating the use of sensitivity analysis to show the impact of variations in important values on the overall results.

Discounting is the process whereby the effect of time passing is incorporated into pharmacoeconomic analysis. Costs and values change with the passage of time, and it is therefore necessary to compensate to allow for this. Discounting converts currency units to their projected future values by applying a 'discount rate', generally accepted as being 5% per annum on costs and 0%, 5% or 6% on benefits. The process reflects society's preference for current benefits over future gains, and results in an annual increase in costs equal to the discounting rate. Discounting is only necessary if the time span of a project is greater than one year.

		Cost		
		Higher	Equal	Lower
Effectiveness	Higher	Possibly	Yes	Yes
	Equal	No	Neutral	Yes
	Lower	No	No	Possibly

Figure 1.7. A typical pharmacoeconomic decision matrix. Each alternative option must be balanced in terms of cost and outcome. In order to be accepted an option must be of equal or lower cost, and preferably equal or greater effectiveness. If an alternative is lower in both cost and effectiveness, it may be implemented if budgetary constraints are significant; if greater in both cost and effectiveness, it may be implemented in the interests of improving patient outcomes (Reeder, 1995).

1.8.5. *Cost of Death*

An important issue is the cost to the state of the malaria-related death of a patient. Direct costs may involve funerals and a number of other factors. Indirect costs are manifold, and include non-remunerated household work (e.g. cooking, collecting wood), as well as the impact of a shortened life expectancy on productive society (e.g. the cost to business of an escalating crime rate). Employed individuals would lose the present value of their lifetime income, although this does not affect the state. It can also be argued that the above indirect costs are offset by the savings made in future healthcare services and unemployment benefits unused by the deceased, but this may perpetuate higher mortality and a lower per capita income, and discourage policy development.

In the case of child mortality, another factor comes into play: the cost to households and society of higher birth rates, which increase concomitantly with increasing infant and child mortality. Costs invested in education, healthcare and women's health will be written off with every death, as potentially productive individuals are lost before maturity.

While a comprehensive analysis of costs related to death was well beyond the scope of this study, its importance cannot be underestimated. It should also be noted that cost of death has little impact on the costs incurred by the public healthcare provider (Donaldson & Shackley, 1997; Kobelt, 1996).

1.8.6. Ethics

There are two opposing schools of thought regarding ethics in pharmacoeconomics. The first proposes that attaching a financial figure to clinical decision-making is potentially unethical.

The second puts forward the idea that all clinical decisions have costs associated with them, and to ignore that fact is unethical, because resources are limited. The use of resources associated with a clinical decision implies that they will no longer be available elsewhere, thus denying them to others.

The argument has been presented (Williams, 1998) that disregarding costs in clinical decision-making is akin to fanaticism.

Chapter 2

AIMS, OBJECTIVES & METHODOLOGY

2.1. Justification for the study

The cost-effectiveness of the treatment of uncomplicated *P. falciparum* malaria with sulfadoxine-pyrimethamine in Mpumalanga was evaluated, giving a crucial measure of the advisability of the change from chloroquine as a first-line therapy. Further, several other alternatives were modelled to assess their suitability for use as first-line treatment.

The basic conceptual framework developed for this study may potentially be applied generally to other infectious diseases, such as HIV/AIDS, sexually-transmitted diseases (STDs), tuberculosis, and cholera.

This information is vital to a number of stakeholders, including the provincial Malaria Control Programme, the provincial and national Departments of Health and Welfare, the World Health Organization, and other researchers.

2.2. Study Design

This is a cost-effectiveness analysis (CEA) of sulfadoxine-pyrimethamine as first-line treatment for *P. falciparum* malaria in Mpumalanga, compared with chloroquine. The direct and, to a limited extent, the indirect costs of treating the disease with sulfadoxine-pyrimethamine and/or chloroquine in Mpumalanga were evaluated. Additionally, the costs of employing other alternative therapies, including the artemisinin derivatives, atovaquone-proguanil, and pyronaridine were modelled.

Resistance to sulfadoxine-pyrimethamine in the South African milieu is thought to be lower than resistance to chloroquine, the first-line agent of choice until the beginning of 1997. The artemisinin derivatives and pyronaridine are presently undergoing clinical trials, and may become available for widespread use soon. Preliminary results are encouraging.

The study was observational in nature, and was located in the Tonga district of Mpumalanga, due to its high malaria transmission between October and April. It was both retrospective and prospective, with data gathered from both hospital and rural clinical settings. Data collected from malaria notifications and an *in vivo* chloroquine effectiveness study conducted in 1997 by the Mpumalanga Malaria Control Programme was used retrospectively. Information was collected from patients regarding income and expenses incurred in travel. Subjects were recruited from two 24-hour district clinics located respectively at Naas and Mangweni. These subjects also participated in a study of sulfadoxine-pyrimethamine effectiveness being carried out by the Malaria Control Programme, similar to the chloroquine investigation conducted in 1996-1997. Information was shared between this study and the effectiveness study; the latter provided follow-up data conforming to WHO guidelines. Mpumalanga Department of Health and Welfare (DOHW) databases containing malaria notification data were extensively used.

The study has been designed to provide information to governmental and health care system decision-makers.

The study was passed by the University of Cape Town Medical School Ethics Committee, as well as the equivalent authority in Mpumalanga. Written informed consent was obtained from all patients participating in the study, under the auspices of the sulfadoxine-pyrimethamine *in vivo* study.

2.3. Aim

The project had the overall goal of estimating the total direct costs of malaria to the public health system and afflicted patients in the Shongwe and Tonga districts of Mpumalanga, in terms of fixed and variable costs, from the perspective of the public health care system.

2.4. Objectives

- Analyse the baseline malaria situation in the area to provide background information, primarily concerning malaria case frequency at clinic and hospital level, in order to justify choice of sentinel sites, and in order to gauge the efficiency of the active surveillance programme in the region.
- Determine the variable and fixed direct costs of treating uncomplicated *P. falciparum* malaria in Mpumalanga province (Shongwe Hospital and district clinics) per malaria case, with respect to the health care system and the individual patient, at primary and secondary health care levels, by means of a model.
- Relate all data to determine the costs and cost-effectiveness of the treatment of uncomplicated *P. falciparum* malaria with a single dose of sulfadoxine-pyrimethamine

with respect to both patient and health care system, compared with treatment of the same class of patient with chloroquine. The average cost-effectiveness ratio (ACER) analysis technique was used.

- Model other treatment approaches, based on effectiveness data obtained from the literature, to evaluate their projected cost-effectiveness.
- Determine the costs of treatment to malaria patients, including travel expenses.
  - Determine mean road distances from the sentinel clinics (Naas and Mangweni) to the communities from which their patients are drawn.
  - Determine mean cost per kilometre travelled per patient, based on information collected by means of the questionnaire.

2.5. Methodology

2.5.1. *Sentinel Sites*

The clinics at Naas and Mangweni were chosen as sentinel sites owing to their 24-hour status, as well as their use as sentinel sites for a study evaluating the *in vivo* resistance of *P. falciparum* to sulfadoxine-pyrimethamine in the district. The latter study was conducted jointly by the South African Medical Research Council's National Malaria Research Programme and the Mpumalanga Department of Health and Welfare's Malaria Control Programme, and assisted with some data gathering for this work.

2.5.2. *Baseline Study of Malaria in the Nkomazi Region*

2.5.2.1. *Thick smear records for assessment of distribution and positivity*

The laboratory based at Shongwe Hospital was, until 1997, responsible for confirming the diagnosis of all malaria cases presenting at any health facility in the Tonga and Shongwe districts. This was done by microscopic examination of blood specimens obtained from patients suspected of having malaria; a droplet of blood was placed on a glass slide as a thick smear and inspected for trophozoites by a skilled microscopist. The presence of trophozoites was taken as confirmation of malaria in the patient. The test was accurate enough to distinguish between species of *Plasmodium*, but diagnostic accuracy was impossible to evaluate and depended heavily on microscopist skill, a serious limitation since skill levels were reportedly low (Durrheim *et al*, 1997).

Records kept at the laboratory covered a period of time between 1991 and 1996. These were analysed to determine:

- The presentation rate of positive cases among public health facilities in the district, in order to identify regions of high transmission;
- The positivity rate at these public health facilities (the proportion of malaria cases positively identified as against the total number of thick smears analysed), to provide an estimate of the ratio of malaria cases to tests performed;
- The relationship between positivity rate at public health care facilities and time of year, in order to assess whether the time of year influenced diagnosis patterns in primary health care staff;
- The positivity rate of thick smears analysed for the active surveillance programme in the region, to assess the usefulness of the programme.

2.5.2.2. *The 1997 malaria notifications database for validation of the thick smear approach*

The Mpumalanga Department of Health and Welfare (DHW) began keeping a more detailed database of malaria notifications in the province in 1997; the 1997 revision contains fields for date, name, race, age, gender, plasmodial species, address, source of infection, notification location and method of detection (both actively and passively detected cases were included). Prior to that year, no information on the site at which the malaria case was detected was kept. A copy of the database was obtained from the DHW and analysed to assess the distribution of notifications among public health care facilities in the Shongwe and Tonga districts. This served as a means of validating the laboratory data on thick smear analysis as a tool for assessing cases that presented at district health care facilities from 1991 to 1996.

The 1997 database was also analysed to determine the proportion of the total number of malaria cases notified in the province made up by notifications from the Nkomazi region. The suitability of the sentinel sites was evaluated by examining the relative malaria caseload at each of the two locations.

2.5.2.3. *Analysis of demographic data*

In addition to the 1997 revision of the DHW's malaria notifications database, a copy of an earlier version of the database, covering 1987 to 1996, was obtained.

The database was analysed with a view to determining the distribution of patients in the Nkomazi region, as well as the entire province, by age, gender, and species of *Plasmodium* from January 1987 to December 1996. The analysis was repeated using data from the revised database, covering January 1997 to December 1997.

2.5.3. *Development of the Model: Comparing Chloroquine and Sulfadoxine-pyrimethamine*

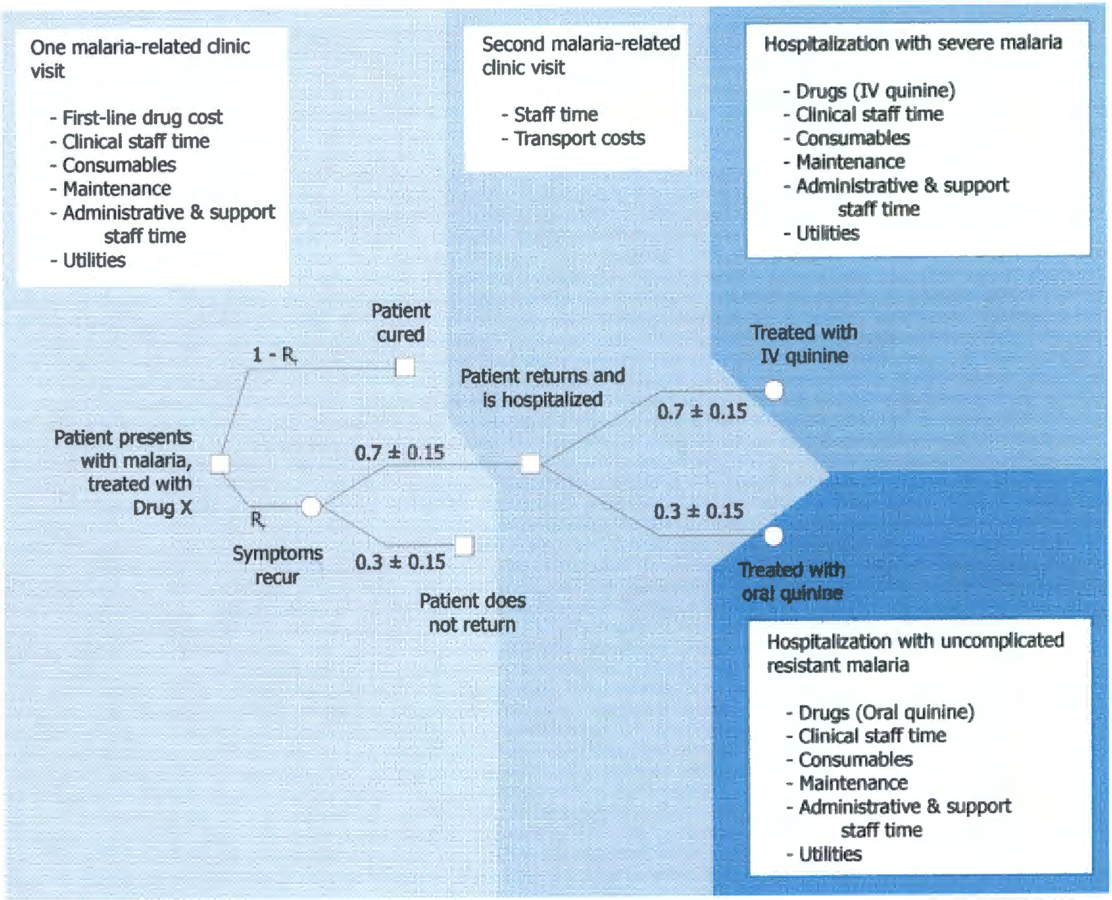


Figure 2.1. Flowchart illustrating the philosophy behind the costing methodology used in this work. South Africans have a lower level of herd immunity in comparison to the populations of other African countries in which malaria is endemic because of seasonal malaria transmission. First-line treatment failure may therefore be more serious, which the Mpumalanga Department of Health and Welfare felt justified their policy of mandatory hospitalisation of treatment failures.

2.5.3.1. *The Resistance Variable (R)*

In order for the direct fixed and variable costs for a first-line drug therapy to be assessed, a model was necessary for each category of cost. The model was in turn developed to be dependent on the concept of a resistance variable (*R*), which is defined as follows:

$$R = P_R \times (P_P \pm 0.15) \qquad 1$$

R describes the proportion of those patients for whom first-line therapy was ineffective that return to the same clinic for further treatment.

P_R, the rate of resistance, was the *in vivo* resistance rate for the drug, including RI, RII and RIII resistance. P_P was the estimated proportion of resistant patients (in whom first-line treatment was a clinical failure) who would return to clinics for further treatment. P_P was taken as 0.70 throughout the region, based upon expert interviews with regional and frontline health professionals (personal communications, D Dürrheim & S Donohue). For sensitivity assessment, it was assumed that a normal distribution was present, with a standard deviation of 0.15. The remainder of the resistant subset of patients were presumed to seek help from the private sector or traditional healers, or not at all. Residents of the district typically have little access to formal private medicine. R is derived under the assumption that there is no resistance bias in those who return to the clinics.

P_R for chloroquine and sulfadoxine-pyrimethamine was obtained from *in vivo* studies of each drug in the Nkomazi district of Mpumalanga in 1996 and 1998 respectively. Both studies made use of a 42-day follow-up period and were strictly controlled. PCR validation was used to control for recrudescence (Govere *et al*, in press).

2.5.3.2. *Modelling Approach*

A system of equations was developed to implement the model, one equation for every category. In order to circumvent the problem of point estimates, a risk-analysis package was used to generate uncertainty in the resistance variable R as well as in the variable describing the proportion of hospital malaria admissions receiving intravenous quinine (R_{IV}). Both variables were described by a normal distribution with a mean of 0.7 and a standard deviation of 0.15.

All the data for all categories was entered into a spreadsheet according to the model. A Monte Carlo simulation consisting of 1 000 iterations was run, using random values for R and R_{IV} that were generated in accordance with the normal distribution. The mean and standard deviations in each category of costs were recorded for each drug, and taken as the best possible estimates of the real costs of each category.

2.5.3.3. *Modelling of Variable Costs*

Variable costs, defined as costs that are subject to change depending on the choice of first-line therapy, include drug costs, the costs of clinical staff time used in malaria treatment, the costs of consumables associated with malaria treatment, and the costs of transporting malaria patients to and from hospital. Equations were developed, using the work of Kirigia *et al* (1997) on the pharmacoeconomics of schistosomiasis treatment as a starting point, for each category of variable cost.

◆ *Drugs*

Drug costs include the costs of the first-line agent itself, as well as the cost of quinine used in treating hospitalised resistant patients. Details of costs were obtained from the Shongwe Hospital pharmacy (personal communications, S Swanepoel, Pharmacist, Shongwe Hospital) in the case of chloroquine, sulfadoxine-pyrimethamine and quinine. Other drugs were valued at the tender prices at which they were available to public health in 1997 (personal communication, M Kiessig, Financial Pharmacist, Groote Schuur Hospital). Those drugs not on tender were valued according to 1997 retail prices (MiMS, 1997). Drugs not registered in South Africa were evaluated either at their international selling price (in the case of artesunate and co-artemether) or at World Health Organisation projected cost (in the case of pyronaridine). Costs of administration were included with staff costs.

The equation for the calculation of drug costs is derived as follows:

$$Cost_{Da} = (C_d . n_{ma}) + R_{IV}[R.n_{ma}(C_{IVQ3} + C_{POQ4})] + (1 - R_{IV})[R.n_{ma}.C_{POQ7}] \qquad 2$$

$Cost_{Da}$ is the total annual cost of using a specific first-line antimalarial drug for the treatment of patients falling within a certain age group (as an indicator of weight, and hence of dose used) at a single site. C_d is the cost of a treatment course at the necessary dosage for the age group, and n_{ma} is the number of patients within the age group treated with the drug during the year. R_{IV} is the proportion of referred patients within the age group receiving intravenous quinine upon hospital admission, and is equal to 70% ± 15% (personal communications, S Donahue & E Athan, Shongwe Hospital; M Young, Bethesda Hospital, KwaZulu-Natal). R is the rate of resistance to the first-line antimalarial. C_{IVQ3}, C_{POQ4}, and C_{POQ7} refer to the costs of quinine given intravenously for 3 days, orally for 4 days, and orally for 7 days, respectively. Gender differences were incorporated via the NCHS Growth Charts (see Fig. 3).

This simplifies to

$$Cost_{Da} = n_{ma}\{C_d + R[R_{IV}(C_{IVQ3} + C_{POQ4}) + (1 - R_{IV})C_{POQ7}]\} \qquad 3$$

So total cost of the drug across all age groups is

$$Cost_D = \sum_{i=1}^{i=a} Cost_{Da} \qquad (4)$$

and cost per patient ($Cost_n$) is

$$Cost_n = \frac{\sum_{i=1}^{i=a} Cost_{Da}}{n_{mi}} \qquad (5)$$

for all the age/dosage differences for a particular first-line drug.

For the calculation of cumulative costs, the resistance variable was used to estimate the number of referrals to Shongwe Hospital from each of the two study clinics. After consultation with senior clinical staff at the hospital, the assumption was made that 70% ± 15% of those referrals were severe enough to require 3 days of intravenous treatment followed by 4 days of oral quinine. The remaining 30% ± 15% of referrals were assumed to be treated with 7 days of oral quinine, but admitted for observation for the first 3 days.

$$Cost_Q = \left(Weight_{NCHS} \times Dose\ per\ kg \times Cost\ per\ mg\right) \qquad (6)$$

$Weight_{NCHS}$ is weight extrapolated from age using the NCHS Growth Charts. *Dose per kg* is (for intravenous quinine therapy) 20 for loading dose and 10 for all subsequent doses. *Cost per mg* is R5.428/300mg, which is R0.018/mg. For oral quinine, *Cost per mg* becomes R0.003/mg. Wastage of intravenous quinine was not considered; it was felt to be negligible, as costs incurred by resiting were assumed to be confined to replacement of the IV apparatus and not the bag.

♦ *Clinical Staff Time*

Clinical staff time refers to the value of time spent by clinical staff in treating and interacting with malaria patients, both at clinic level and at the district hospital. Clinical staff include doctors and nurses, those who are directly involved with patient treatment. The value of their time was calculated by estimating the amount of time spent on patients and valuing that time based upon their 1997 annual salaries and benefits, as supplied by the Mpumalanga Department of Health and Welfare (personal communication, R Raubenheimer).

Clinical staff time costs are made up of two primary components: staff time at clinic level and staff time at hospital level.

$$Cost_{CSi} = n_{mi}(1 + R) \times Time_{ci} \times S_{ni} \qquad 7$$

$Cost_{CSi}$ is the contribution to costs made by clinical staff time. n_{mi} is the number of malaria notifications at the clinic, R is the resistance variable for the study drug, $Time_{ci}$ is the time per malaria consultation (10 min), and S_{ni} is the salary per minute of the consulting clinic nurse.

$$Cost_{HSi} = 3Rn_{mi}\{[R_{IV}(D_{TIV}.S_{di} + N_{TIV}.S_{ni})] + [(1 - R_{IV})(D_{TO}.S_{di} + N_{TO}.S_{ni})]\} \qquad 8$$

$Cost_{HSi}$ is the clinical staff cost of referred malaria at Shongwe Hospital in 1997. R is the resistance variable, n_{mi} is the total number of malaria notifications for 1997, R_{IV} is the proportion of referred patients receiving intravenous quinine therapy, D_{TIV} is the amount of time spent daily (in minutes) on each malaria patient by medical officers, S_{di} is the salary per minute of a medical officer, N_{TIV} is the amount of time spent daily (in minutes) on each malaria patient by nursing staff, and S_{ni} is the salary per minute of an average nursing staff member at Shongwe Hospital. D_{TO} is the time spent daily (in minutes) on a malaria patient requiring oral quinine by medical officers, and N_{TO} is the time spent by nursing staff on the same type of patient.

Total costs are described by equation (9):

$$Cost_{TSi} = Cost_{CSi} + Cost_{HSi} \qquad 9$$

- *Consumables*

Consumables describe items with a lifespan of less than one year; items such as disposable gloves, syringes, IV bags, canulas, and ICT kits. Malaria cases were monitored for the duration of their stay in hospital to determine what consumables were used on a standard malaria admission. Costs were based on those quoted by the Shongwe Hospital pharmacy (S Swanepoel). ICT kits are used systematically for the diagnosis of malaria, owing to the poor reliability and delay associated with microscopy (Durrheim *et al*, 1997), and were valued according to their South African tender price.

Costs were calculated with the aid of equation (10):

$$Cost_C = \left(\frac{n_{mi}}{R_p} \times C_f \right) + R.n_{mi} \left[R_{IV} \left(C_{IV3} + C_f \right) + (1 - R_{IV}) C_f \right] \tag{10}$$

$Cost_C$ is the total consumables cost stemming from malaria cases initially treated with the first-line agent under investigation during a single year. The number of malaria patients presenting at a study clinic (n_{mi}) is extrapolated upwards to estimate the total number of malaria tests carried out at the clinic. This estimation is obtained by dividing n_{mi} by R_p, the positivity rate for the clinic, determined from Shongwe Hospital laboratory records of smears conducted between 1991 and 1996. The quotient is multiplied by C_f, the average consumables cost of a single ICT-based malaria test, to generate the total cost of consumables used in malaria testing at the clinic. Since no other malaria-related activity is carried out at clinic level, this is the total malaria-related cost of consumables at the clinic for the year.

The second term of the equation refers to the contribution made to the cost of consumables by hospital admissions. R is the resistance variable, R_{IV} is the proportion of clinic malaria referrals that receive 3 days of intravenous quinine upon admission, and C_{IV3} is the average cost of consumables used during 3 days of IV quinine therapy. All referred patients are routinely re-tested upon admission, and therefore use another ICT and other test-related items included in C_f. Patients admitted for oral therapy are assumed to use no other consumables, except food. Glucose monitoring is not routinely done in rural hospitals.

Consumables used at clinic level in the first-line treatment of malaria include immunochromatographic testing (ICT) kits, cotton wool swabs, lancets, alcohol swabs, and non-sterile pairs of gloves. Each patient tested for malaria is assumed to use one of each of these. While laboratory-based blood tests were used for part of 1997, it is assumed for the purposes of modeling that ICTs were used throughout.

Since patients are not admitted to the clinics, no other consumables are used, with the exception of stationery, which for the purposes of this study are assumed to be negligible.

Once admitted to hospital for intravenous quinine therapy, consumables used would include IV kits, drip bags, disposable gloves, cotton wool swabs, and meals. Patients receiving oral quinine are assumed to use no consumables apart from food and an ICT upon discharge. Food, however, as is the case with linen, was common to all patients (Coyle, 1996).

◆ *Transport*

Transport costs are those incurred in the process of transporting patients from clinic to hospital. These costs applied only to hospital admissions, and were mainly limited to fuel costs. Vehicles were taken to be capital items, and vehicle maintenance was not considered.

The transport costs of first-line treatment of malaria are confined to the costs involved in transporting referred patients from the outlying clinics to Shongwe Hospital. The informal ambulance service is composed of a number of four-wheel-drive vehicles that run between several clinics each and Shongwe Hospital. Transport costs involved in training have been incorporated in the in-service training component. The equation is:

$$Cost_T = R.n_{mi} \times Dist_i \times C_o \qquad 11$$

$Cost_T$ is the total transport cost generated by patients originating at a study clinic *i*, Rn_{mi} is the number of malaria patients referred for hospital treatment by clinic *i*, $Dist_i$ is the distance that must be covered by an ambulance vehicle while collecting referred patients and transferring them to the hospital, and C_o is the mean operating cost per kilometre of the vehicles performing the function.

2.5.3.4. *Modelling of Fixed Costs*

Fixed costs describe those costs that do not change when a new first-line therapy is introduced. Change in costs of this kind may only be reasonably expected when a threshold number of patients is reached and existing infrastructure can no longer cope with demand. They include capital costs, maintenance of equipment and facilities, time of administrative and support personnel, in-service training of staff, and utilities such as water, electricity, postage and telephone calls. In all cases, it was assumed that the proportion of each cost per clinic assigned to malaria would be equal to the proportion of malaria patients to total patients at each study clinic.

Due to inherent difficulties in the adaptation of a ratio approach to fixed costs – adoption of a more effective therapy would reduce patient load, and hence increase the proportion of each fixed cost allocated to malaria, rather than reducing it – fixed costs were also examined in terms of savings in clinic visits and hospital days.

◆ *Adjustment of n_i and n_h*

Since sulfadoxine-pyrimethamine was used from the beginning of 1997 onwards, it was assumed that the hospital and clinic totals (total patients seen for the clinics and total admissions for the hospital) included patients returning for further treatment upon the failure of sulfadoxine-pyrimethamine. Therefore, the clinic and hospital total patient loads (n_i and n_h respectively) were moderated as follows for drug *x*:

$$n_i = n_i + \left(R_x n_{mi} - R_{SP} n_{mi}\right) \qquad 12$$

◆ *Capital*

Capital items are fixed items required by a health facility, including buildings, furniture, and equipment. Acquisition of new equipment or replacement of existing assets is not envisaged to occur when a new first-line drug is adopted; hence, capital costs are disregarded for the purposes of this study.

◆ *In-service Training*

In-service training in malaria-related matters occurs annually in the Nkomazi region. It is not directly dependent on first-line drug therapy. Details of costs (which included salaries of involved staff and transport costs) were estimated based upon information obtained from the Mpumalanga Department of Health and Welfare (D Dürrheim) on training courses conducted annually in the district. However, since this cost is identical no matter the choice of first-line therapy, it is largely irrelevant to cost-effectiveness.

The equation for this aspect of costs is as follows:

$$Cost_{IST} = \left[Q_{Ti} \times Day_{Ti} \times \left(\frac{S_{ci}}{365.25} + C_{Ti} \right) \times R_{Ti} \right] \tag{13}$$

In-service training in malaria management for private doctors, provincial doctors and nurses is provided every year (D Dürrheim). Variables used include the number of staff of type i involved (Q_{Ti}), length of the training sessions (Day_{Ti}), average cost of training per trainee per day (made up from salary cost per day ($S_{ci}/365.25$) and cost of training-related consumables per day of training (C_{Ti})) and proportion of training allocated to malaria (R_{Ti}) are assumed to be independent of the drug therapy selected.

◆ *Maintenance*

Maintenance costs are those related to the upkeep of equipment and facilities; examples include replacement of broken windows and repairs to facilities. Responsibility for maintenance of public health facilities lies with the Department of Public Works, but records are kept at district level by the Department of Health and Welfare (S Mabuza, Eerstehoek-Carolina District).

The equation for maintenance costs is as follows:

$$Cost_M = (1+R)\left(\frac{n_{mi}}{n_i}\right)M_{ci} + R\left(\frac{n_{mi}}{n_h}\right)M_h \qquad (14)$$

$Cost_M$ is the total annual maintenance cost of treating malaria cases detected at a study clinic with a first-line antimalarial drug. R is the drug's resistance variable, n_{mi} is the number of malaria cases presenting at the clinic during one year, n_i is the total number of patients visiting the clinic during the same year, and M_{ci} is the annual maintenance cost for clinic i. n_h is the total number of hospital admissions during the year, and M_h is the annual cost of maintenance at this district hospital.

♦ *Administrative & Support Staff Time*

Administrative and support staff are those cadres not directly involved in the treatment of malaria, including clerks, cooks and sanitation staff. In contrast to clinical staff time, the overall contribution of administrative and support staff to total costs was assessed by applying the same malaria case ratio used in the calculation of the other fixed costs to their cumulative annual salary including benefits. Details of annual salaries and benefits were obtained from the Department of Health and Welfare (R Raubenheimer).

The equation for this aspect of fixed costs follows a similar pattern to equation (14):

$$Cost_S = (1+R)\left(\frac{n_{mi}}{n_i}\right)S_{ci} + R\left(\frac{n_{mi}}{n_h}\right)S_h \qquad (15)$$

$Cost_S$ is the total annual administrative and support staff cost of treating malaria cases detected at clinic level with a first-line antimalarial drug. R is the drug's resistance variable, n_{mi} is the number of malaria cases presenting at the clinic during one year, n_i is the total number of patients visiting the clinic during the same year, and S_{ci} is the combined annual salary of all staff in the support and administrative categories. n_h is the total number of hospital admissions during the year, and S_h is the combined annual salary of all hospital support and administrative staff.

It was assumed that all support and administrative staff at both clinic and hospital level contributed to the treatment of malaria, regardless of specific job description, in equal proportion to the ratio of malaria cases to non-malaria cases. This is justified if one considers that the overall aim of any healthcare facility is to treat patients: all staff ultimately contribute towards this, regardless of the degree with which they are directly involved with patients.

◆ *Utilities*

Utility costs include annual totals for water, electricity, postage, and telephone calls at each of the two study clinics, also taking those of the district hospital into account. No public health care facility is responsible for the payment of water accounts. Cost information was provided by the Tonga and Shongwe district offices (A Khoza, Tonga; D Nkosi, Shongwe).

The equation is based upon the number of patients serviced by the clinics as a proportion of the total number of patients visiting the clinics.

$$Cost_U = (1+R)\left(\frac{n_{mi}}{n_i}\right)U_{ci} + R\left(\frac{n_{mi}}{n_h}\right)U_h \qquad (16)$$

$Cost_U$ is the total cost of utilities at 24-hour clinic *i*. *R* is the resistance variable, n_{mi} is the number of notified malaria patients presenting at the clinic during a period of 1 year, U_{ci} is the cost of utilities at clinic *i*, n_i is the total number of patients seen per annum at clinic *i*, U_h is the total utilities cost at hospital *h*, and n_h is the total number of admissions at hospital *h*. Structurally, the equation is identical to equation (14).

2.5.4. *Modelled Costs of Alternative First-line Antimalarial Drugs*

Probability of resistance for the other modelled drugs was estimated from data on their *in vivo* efficacy in Sub-Saharan Africa obtained from a thorough literature search using MEDLINE. Inclusion criteria were somewhat relaxed: randomised controlled trials (RCTs) conducted in sub-Saharan Africa were preferred, followed by *in vitro* sensitivity studies, followed by RCTs conducted elsewhere in the world. Large sample sizes were also desirable. An *R* value was then calculated for each from equation (1) and each drug was modelled in the same manner as chloroquine and sulfadoxine-pyrimethamine, using chloroquine as a comparator.

Drugs and drug combinations modelled included amodiaquine, artesunate, artesunate-mefloquine, atovaquone-proguanil, co-artemether, halofantrine, mefloquine and pyronaridine. Quinine combinations were also considered, but their cinchonistic side effects and long treatment courses were thought to make them unsuitable for first-line treatment in a rural African setting.

2.5.5. *Assessing cost-effectiveness of alternative antimalarial drugs*

The average cost-effectiveness ratio (ACER) for drug i was assessed by means of equation (17). For chloroquine, the ACER will always be equal to 1.0. This will be true as long as an identical outcome—in this case patient cure—is obtained.

$$ACER = \frac{Mean\ Total\ Cost\ per\ Patient\ of\ Baseline\ Drug\ (Chloroquine)}{Mean\ Total\ Cost\ per\ Patient\ of\ Modelled\ Drug} \quad 17$$

The drug and dosage cost data were related to the number of recrudescences detected among the study group by the follow-up personnel, in order to draw conclusions regarding the effectiveness of each drug.

2.5.6. *Treatment Costs Incurred by Patients*

2.5.6.1. *Data Collection*

Mpumalanga Malaria Control Programme staff at the 24-hour clinics at Naas and Mangweni assisted patients with the completion of forms, in co-operation with clinic personnel, under the auspices of the *in vivo* sulfadoxine-pyrimethamine resistance study.

2.5.6.2. *Patient Information*

Patients were recruited according to the inclusion and exclusion criteria specified by the Mpumalanga Malaria Control Programme's protocol for the *in vivo* study of sulfadoxine-pyrimethamine resistance in South Africa's malaria areas (la Grange *et al*, 1998). Each recruited malaria patient (or their legal guardian) was issued with a questionnaire designed to gather data regarding the patient's personal details and travel information. These data were used to assess the direct financial impact of malaria on patients.

2.5.6.3. *On-site Evaluation of Data*

Diagnosis was carried out according to usual clinical procedure at the sentinel site, which was and is by means of a *P. falciparum* immuno-chromatographic test (ICT), a method of high specificity and sensitivity (Dürrheim *et al*, 1998). This was the case for all patients enrolled in the *in vivo* study; notified patients included in the database before 1998, however, were detected by thick smear analysis at the Shongwe Hospital laboratory in the overwhelming majority of cases.

2.5.6.4. *Determination of Travel Costs per Kilometre*

Patient address information in the malaria notification databases assembled by the Mpumalanga Department of Health and Welfare between 1991 and 1997 was retrieved and analysed by clinic to determine numbers of patients from each community visiting the clinics for antimalarial treatment. Mean distances travelled per patient were calculated using the resultant data on feeder areas for the clinics.

Using questionnaires (Appendix B) filled out by clinic assistants during the course of the study, data was collected regarding the costs of travel to each of the 125 participants in the *in vivo* sulfadoxine-pyrimethamine study conducted by the Department of Health and Welfare. The patient group was broken down according to mode of travel (e.g. walking, hired vehicles, private vehicles). A mean travel cost per kilometre was calculated for the group.

Finally, the mean cost of treatment per patient was calculated, comparing chloroquine and sulfadoxine-pyrimethamine as first-line treatments for malaria.

2.5.7. *Statistical Design*

Since much of the work relied on the calculation of point estimates, normal statistical techniques did not apply. Instead, a rigorous sensitivity analysis was conducted, including a risk-based simulation of each drug (Briggs *et al*, 1994; Doubilet *et al*, 1985). A parametric approach was used to evaluate and compare those sections of the collected data for which orthodox analysis was possible. Nonparametric tests are not ideal in economic analysis; the relative values of each observation, and specifically a comparison of the mean values for each alternative, are of primary interest. This is necessary to compensate for patients consuming a disproportionate quantity of resources (Drummond *et al*, 1994).

Probabilistic sensitivity analysis was conducted on each modelled drug, using the Monte Carlo simulation approach. The Monte Carlo simulation selects random values from a specified distribution and records the modelled result for large numbers of hypothetical patients (Briggs *et al*, 1994).

A risk analysis package was used as an alternative to the generation of point estimates. Instead of using a static R value, R was modelled using a normal distribution for estimating the number of returning patients (μ=0.7, σ=0.15). Further, R_{IV} was similarly modelled using the same mean and standard deviation parameters. The simulation was run 1 000 times for each drug, generating a range of values for R and R_{IV} along their respective (and separately modelled) distributions. This resulted in the generation of mean values for each cost category, along with standard deviations and variances.

Individual resource items and effectiveness values are not independent. When analysing pharmacoeconomic data, statistical testing of differences in costs should be primarily focussed on the total costs of the alternatives being compared. The only exceptions to this rule are costs common to all regimens, those that exhibit no variation between patients (Coyle, 1996).

Testing for statistical significance of incremental cost per outcome should only be done if differences between both costs and outcomes are statistically significant (O'Brien & Drummond, 1994).

Recently, suggestions have been made that confidence intervals should be used in preference to simple hypothesis testing in medical research, since the latter provides only a fundamental 'yes/no' result where more detailed information on the imprecision of study estimates is desirable. The main focus in studies of this kind would hence be on precision of measurement rather than statistical significance. This is equally true in economic studies, in which the magnitude of differences between compared interventions is often more important than simply knowing that one intervention is more effective and/or costly than another (Coyle, 1996).

2.5.8. *Appropriateness of the Approaches Used*

2.5.8.1. *Patient Information and Recruitment*

A narrow, highly focused approach was used throughout the areas of the study in which patient information was gathered. Only patients admitted to the Mpumalanga section of the study of *in vivo* sulfadoxine-pyrimethamine resistance were used, due to a number of reasons. The most important was the extreme shortage of clinical staff at the two sentinel clinics; extra clerical work required of the nursing staff was deemed an unacceptable burden by local district management. Additionally, there was considerable opposition to the idea of a second study from the clinical staff themselves, as it was perceived as a further disruption of their normal activities. However, the *in vivo* study was conducted with full district and staff cooperation, and therefore it is unlikely that personnel dissatisfaction was a source of bias.

Chapter 3

BASELINE STUDY OF MALARIA IN THE NKOMAZI REGION OF MPUMALANGA

3.1. 1991-1996 by Thick Smear

The prevalence of malaria in South Africa increased dramatically between January 1991 and December 1996 (Fig. 1.2, p 3). All the smears collected for routine malaria diagnosis at clinics and Shongwe Hospital found to be positive for malaria were listed in laboratory records as *Plasmodium falciparum* infections. The seasonality of malaria in the Mpumalanga Lowveld region was confirmed, with peak transmission being found between December and April (see Figure 1). A substantial increase was found in positive smears in 1996, corresponding with the malaria epidemic experienced by the region in that year (personal communication, Dr D Dürrheim, Infectious Diseases Consultant for the Mpumalanga Department of Health).

Thick smears found to be positive for malaria were categorised by site, and these results appear in Figure 2. Shongwe Hospital showed the largest proportion of positive smears, accounting for an annual mean of 57.69% ± 2.43%. The 24-hour clinics at Naas and Mangweni accounted for mean proportions of the annual total of 7.71% ± 1.24% and 6.66% ± 1.11% respectively. Of the day clinics, Block B, Mbuzini, Steenbok, Sihlangu, Mzinti, and Block C showed the highest proportions of positive smears, ranging between 6.15% ± 1.39% at Block B to 1.03% ± 0.36% at Block C. All the other day clinics had less than 1% of the mean annual total.

In terms of absolute numbers within the six-year period, Shongwe Hospital accounted for 53.63% (2363 positive smears), Naas for 10.10% (445 positive smears), Steenbok for 7.74% (341 positive smears), Mbuzini for 6.42% (283 positive smears), Mangweni for 6.22% (274 positive smears) and Block B for 3.84% (169 positive smears). The balance of these results appears in Table 1.

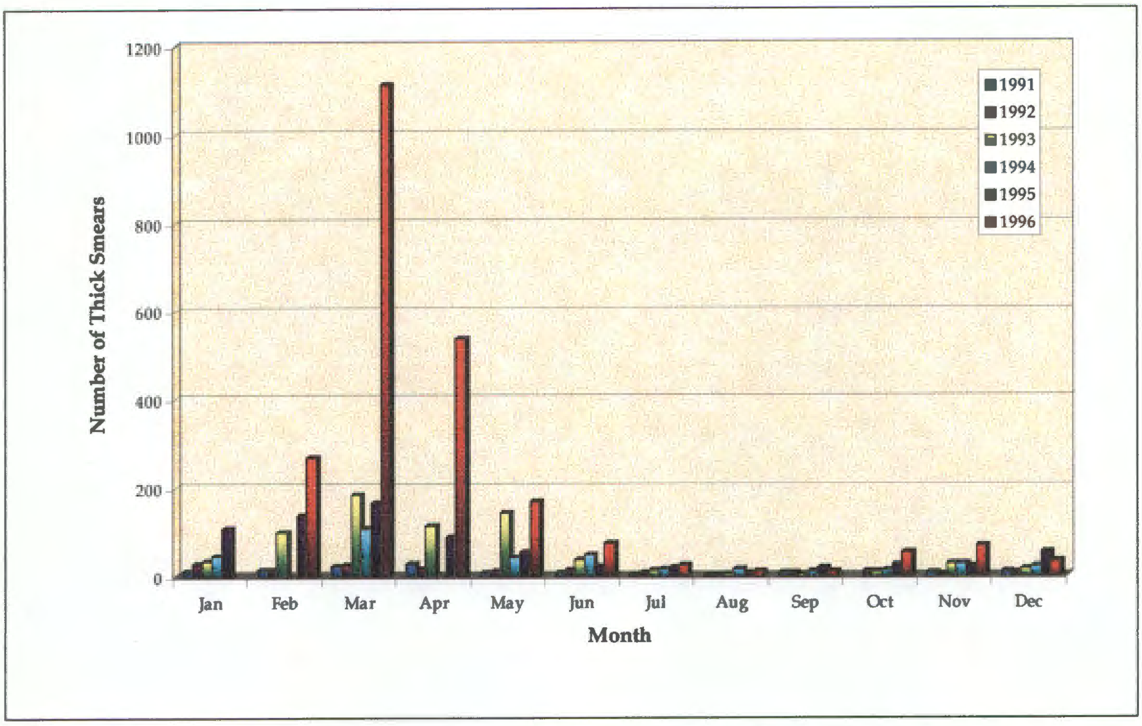


Figure 3.1. Increase in number of malaria cases in the Shongwe and Tonga districts of Mpumalanga between January 1991 and December 1996, based upon blood smear records at the laboratory at Shongwe Hospital.

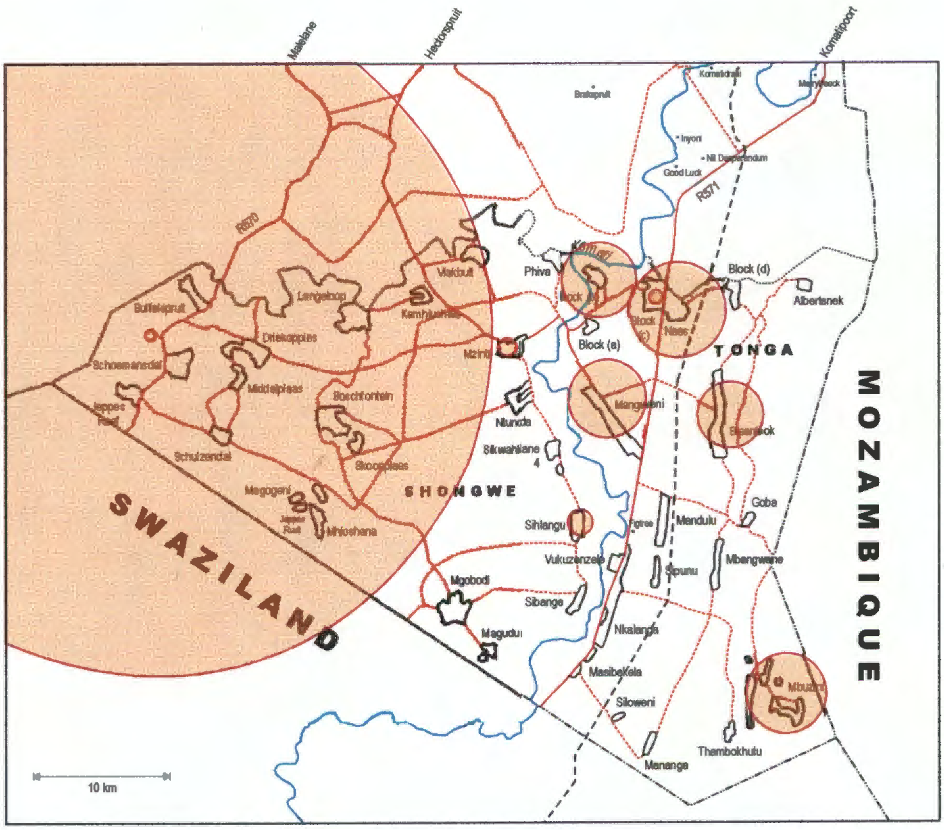
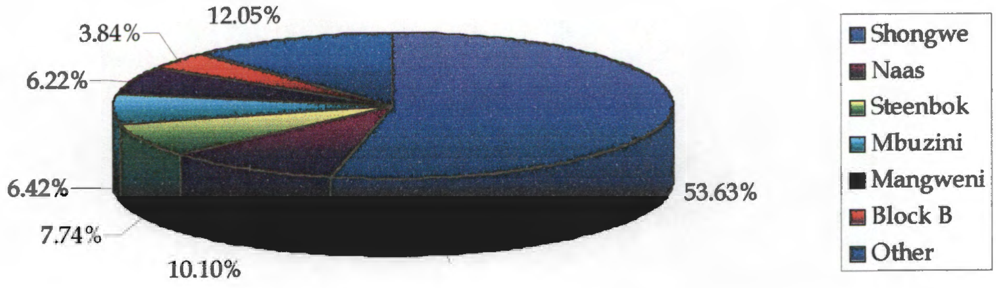


Figure 3.2. Mean frequency of positive malaria diagnoses at clinic level in the Shongwe and Tonga districts of Mpumalanga between 1991 and 1996. Radii of the red shaded areas represent proportion of malaria cases: the 24-hour clinics at Naas and Mangweni have the greatest number of new cases. Shongwe Hospital accounts for the overwhelming majority of cases. All data is based upon blood smear records.

(a) Positive



(b) Total

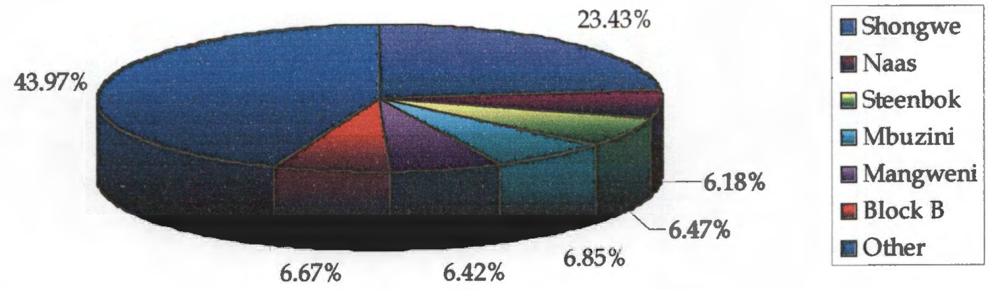


Figure 3.3. The distributions of (a) thick smears found to be positive for Plasmodium trophozoites, and (b) total numbers of thick smears submitted for analysis, including both positives and negatives.

3.2. Positivity of Blood Smears

The efficiency of the blood smear analysis technique was found to be low in most cases, as illustrated in Table 3.1.

Facility	Total smears	Total positives	Proportion of malaria cases	Mean positivity rate
Shongwe	21077	2363	53.63%	11.21%
Naas	5560	445	10.10%	8.00%
Steenbok	5817	341	7.74%	5.86%
Mbuzini	6162	283	6.42%	4.59%
Mangweni	5777	274	6.22%	4.74%
Block B	5996	169	3.84%	2.82%
Sihlangu	3425	84	1.91%	2.45%
Mzinti	4065	59	1.34%	1.45%
Block C	3855	55	1.25%	1.43%
Masibekela	2060	54	1.23%	2.62%
Fig-Tree	2872	48	1.09%	1.67%
Phiva	1458	45	1.02%	3.09%
Mbangwane	168	42	0.95%	25.00%
Mgobozi	4325	42	0.95%	0.97%
Sikwahlane	1359	28	0.64%	2.06%
Middelplaas	2550	22	0.50%	0.86%
Schoemansdal	2583	13	0.30%	0.50%
Langeloop	2259	12	0.27%	0.53%
Kamhlushwa	1406	11	0.25%	0.78%
Jeppes Rust	4239	9	0.20%	0.21%
Boschfontein	1096	5	0.11%	0.46%
Driekoppies	1246	1	0.02%	0.08%
Jeppes Reef	248	1	0.02%	0.40%
Krombraai	24	0	0.00%	0.00%
Makoko	24	0	0.00%	0.00%
Mooiplaas	120	0	0.00%	0.00%
Tjakastad	24	0	0.00%	0.00%
Vlakplaas	144	0	0.00%	0.00%
Total	**89939**	**4406**	**100%**	**4.90%**
Total (without Shongwe)	**68862**	**2043**	**46.37%**	**2.97%**

Table 3.1. Diagnosis of malaria by blood smear at primary health care facilities in the Shongwe and Tonga districts of Mpumalanga. These are the total number of thick smears analysed at the laboratory at Shongwe Hospital from January 1991 to December 1996. Data for October 1991, February 1994, April 1994 and January 1996 were not available and have been omitted from the analysis above.

Year	Months available	Total smears	Total positives	Mean positivity
1991	11	53878	534	0.991%
1992	12	86280	324	0.376%
1993	12	77635	156	0.201%
1994	10	51985	106	0.204%
1995	12	64101	130	0.203%
1996	11	70957	389	0.548%
Total	**68**	**404836**	**1639**	**0.405%**

Table 3.2. Efficiency of the active surveillance programme in the Shongwe region of Mpumalanga, 1991-1996. These data are based on thick smears evaluated at Shongwe Hospital during this period, and the calculations are based on the ratio between smears evaluated and positive diagnoses for *P. falciparum* malaria.

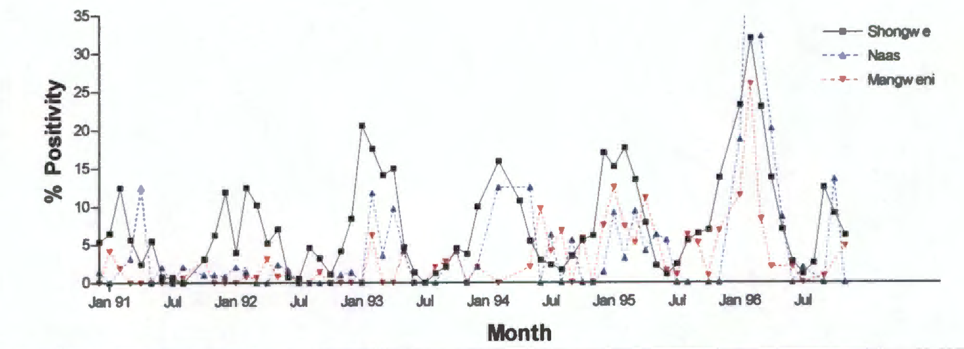


Figure 3.4. Positivity of thick smears obtained from Shongwe Hospital and the 24-hour clinics at Naas and Mangweni during the period January 1991–December 1996.

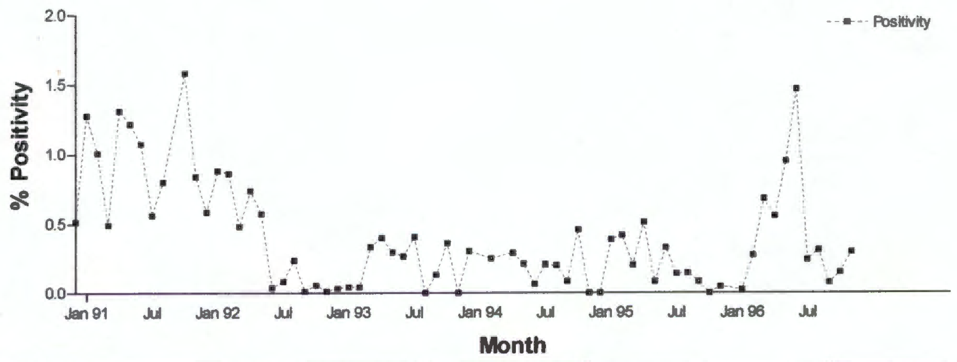


Figure 3.5. Positivity of thick smears analysed at Shongwe Hospital, under the auspices of the active surveillance programme, between January 1991 and December 1996.

3.3. The Malaria Notifications Databases

Results obtained from searching the database for 1997 indicated that the use of clinic thick smear results as a measure of numbers of malaria cases was justified, as results fit within the standard deviations of the figures determined from the 1991-1996 data (Table 3). The primary exception to this is Shongwe Hospital, which accounted for 26.19% (642) of the 2451 notifications recorded among the Tonga and Shongwe clinics in 1997, in contrast to the 53.63% found for the thick smear approach used for evaluating 1991 to 1996. This is partially explained by the routine re-testing of hospital referrals at Shongwe, due to poor communication between the hospital and the referring clinic, as well as slow smear analysis at the laboratory (personal communication, Dr E Athan).

Mbuzini Clinic was the largest single source of notifications in the subregion (after Shongwe Hospital) in 1997, with 22.36% of the total (548 malaria cases). The day clinics at Steenbok and Mbangwane accounted for higher-than-average numbers of notifications, with 7.14% (175 cases) and 7.06 % (173 cases) of the total, respectively. Malaria cases among the sites included amounted to 2451, which constituted 41.31% of the absolute number of cases reported in Mpumalanga in 1997 (5933). However, of these, 23.68% (1405) database entries did not specify location of notification. Although this substantial dataset undoubtedly contains data belonging to the study group, it was necessary to omit it from analysis.

Facility	Proportion of malaria cases by blood smear, 1991-1996	Proportion of malaria cases by notification database, 1997	Difference in proportion	Standard Deviation
Shongwe	53.63%	26.19%	(27.44%)	19.40%
Block B	3.84%	2.12%	(1.72%)	1.22%
Block C	1.25%	1.51%	0.26%	0.18%
Boschfontein	0.11%	0.04%	(0.07%)	0.05%
Driekoppies	0.02%	1.57%	1.55%	1.10%
Fig-Tree	1.09%	4.24%	3.15%	2.23%
Jeppes Reef	0.02%	0.08%	0.06%	0.04%
Jeppes Rust	0.20%	0.04%	(0.16%)	0.11%
Kamhlushwa	0.25%	0.04%	(0.21%)	0.15%
Krombraai	0.00%	0.00%		
Langeloop	0.27%	0.29%	0.02%	0.01%
Magudu	0.00%	0.12%	0.12%	0.08%
Makoko	0.00%	0.00%		
Mangweni	6.22%	11.06%	4.84%	3.42%
Masibekela	1.23%	4.08%	2.85%	2.02%
Mbangwane	0.95%	7.06%	6.11%	4.32%
Mbuzini	6.42%	22.36%	15.94%	11.27%
Mgobodi	0.95%	0.41%	(0.54%)	0.38%
Middelplaas	0.50%	0.61%	0.11%	0.08%
Mooiplaas	0.00%	0.00%		
Mzinti	1.34%	0.78%	(0.56%)	0.40%
Naas	10.10%	9.63%	(0.47%)	0.33%
Phiva	1.02%	0.20%	(0.82%)	0.58%
Schoemansdal	0.30%	0.33%	0.03%	0.02%
Sihlangu	1.91%	0.86%	(1.05%)	0.74%
Sikwahlane	0.64%	0.20%	(0.44%)	0.31%
Steenbok	7.74%	7.14%	(0.60%)	0.42%
Tjakastad	0.00%	0.00%	N/A	N/A
Vlakplaas	0.00%	0.00%	N/A	N/A
Total	**100%**	**100%**		
Total (without Shongwe)	**46.37%**	**73.81%**		

Table 3.3. Comparison of malaria caseload proportions using (a) thick smears between 1991 and 1996 and (b) using data retrieved from the 1997 malaria notifications database maintained by the Mpumalanga Department of Health and Welfare.

3.4. Suitability of Sentinel Sites

The day clinics at Mbuzini and Steenbok receive the highest numbers of malaria patients in relation to other clinics in the Shongwe and Tonga districts. Their malaria caseloads were compared with those of Naas and Mangweni to confirm the suitability of the latter 24-hour clinics as sentinel sites (Fig. 6). Total caseload for Mbuzini in 1997 was 3.91% of total cases, which translates to 5.79% when adjusted for a 47.92% chloroquine resistance rate. Steenbok showed a corrected malaria caseload of 2.29% in 1997.

In comparison, Naas and Mangweni Clinics showed corrected malaria caseloads of 0.78% and 1.10% respectively. While Mbuzini and Steenbok both have higher percentages of malaria cases, they are open only 8 hours a day and lack the infrastructure for hosting studies of this magnitude.

3.5. Demographics

The Mpumalanga Department of Health and Welfare's malaria notifications database, covering January 1987 to December 1996, was searched for details regarding the ages and gender of malaria notifications. Notifications from the entire Nkomazi region of Mpumalanga were included, rather than the clinics considered in the analysis of thick smears, because notification site was only recorded from 1997. A smaller, separate analysis was made of the cases notified between January 1997 and March 1998.

3.5.1. Malaria in the Nkomazi Region, 1987-1996

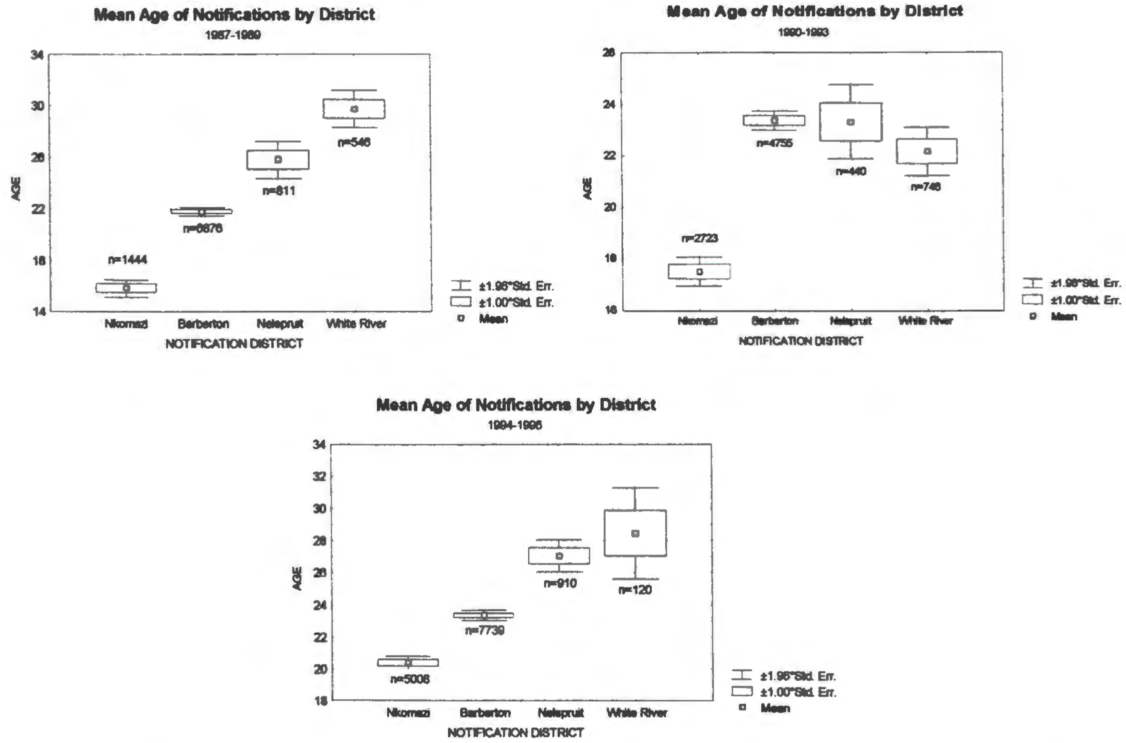


Figure 3.6. Mean ages of malaria patients in the districts of Nkomazi, Barberton, Nelspruit and White River. The analysis was split into three time segments, 1987-89, 1990-93, and 1994-96.

The mean age of the 9 196 notified malaria patients in the Nkomazi district was significantly lower than mean age in other districts in the province ($P < 0.0001$) during the period 1987-1996 (Fig 3.6). The overall mean for this ten-year period was 18.82 ± 0.16 years. Ages ranged between 0 and 101 years, and median age was 15 years. There was a significant increase in age of malaria patients between 1987 and 1996 (Fig 7); slope was significantly different from zero ($m=0.594 \pm 0.166$, $P=0.0073$) but was not linear ($r^2=0.614$).

4 811 (52.32%) of the notifications during this time were female, while 4 385 (47.68%) were male. There were 31 recorded deaths (0.34%).

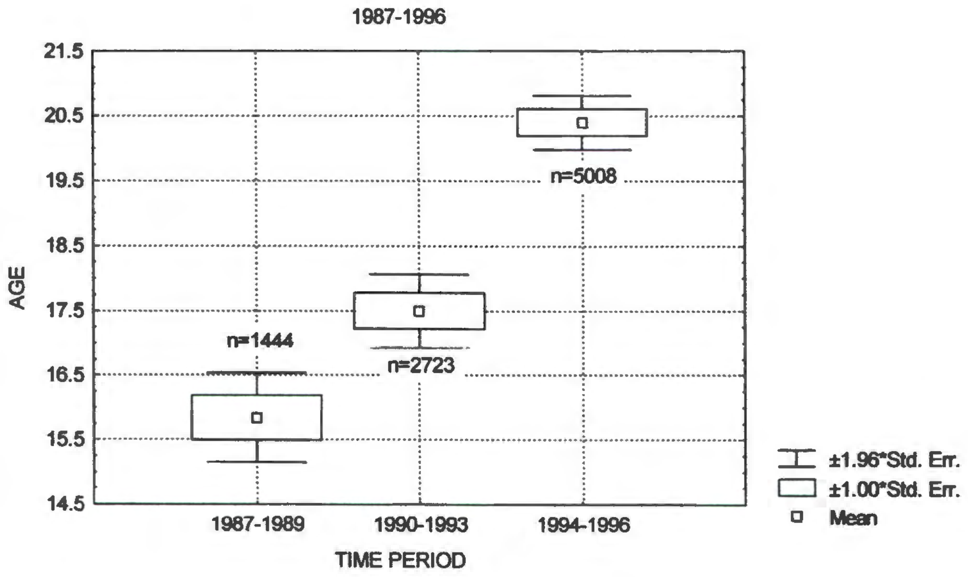


Figure 3.7 (a)

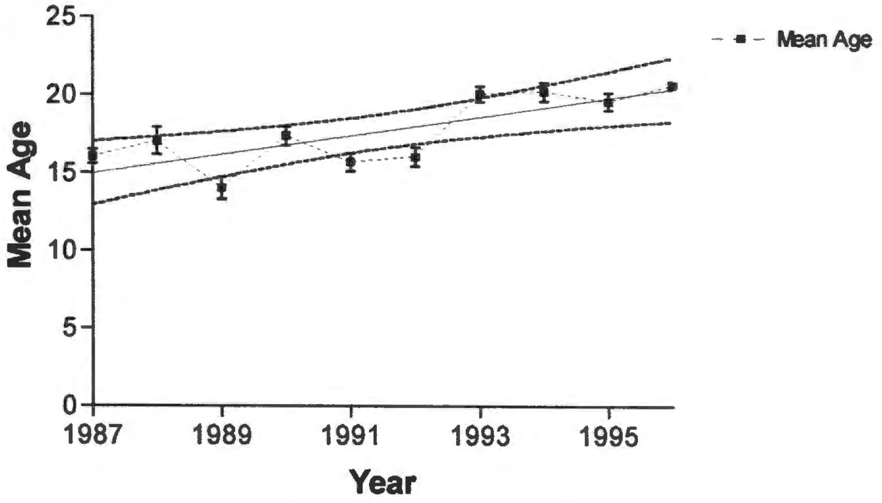


Figure 3.7 (b)

Figure 3.7. Change in mean age of malaria notifications in the Nkomazi region of Mpumalanga between 1987 and 1996.

3.5.2. Malaria in the Shongwe and Tonga Districts, January 1997--March 1998

More than half of the 3 303 usable malaria notifications in the Nkomazi region were under the age of 17 years (53.77%, 1 776 cases). 240 (7.27%) were younger than 3 years, while 69 (2.15%) were 65 or older.

The mean age was 20.21 ± 0.27 years, the median age was 16, and all ages fell between 0 and 95 years. The 1 414 unclassified cases had a mean age of 21.41 ± 0.36 years, and ranged between 0 and 78 years. Male patients made up 50.20% of the Shongwe/Tonga group. Female patients accounted for 49.80%. 15 patients (0.45%) died. Virtually all the patients (3298, 99.85%) were African.

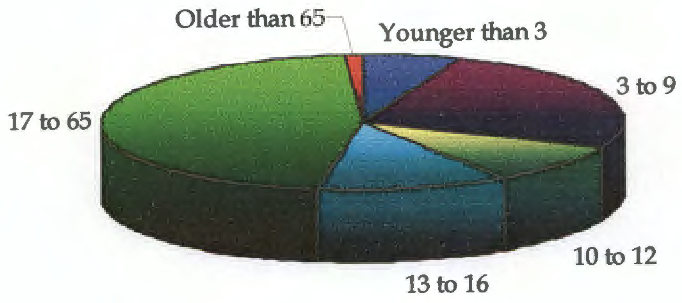


Figure 3.8. Breakdown of malaria notifications in the Nkomazi district by age, during the time period 1987-1996.

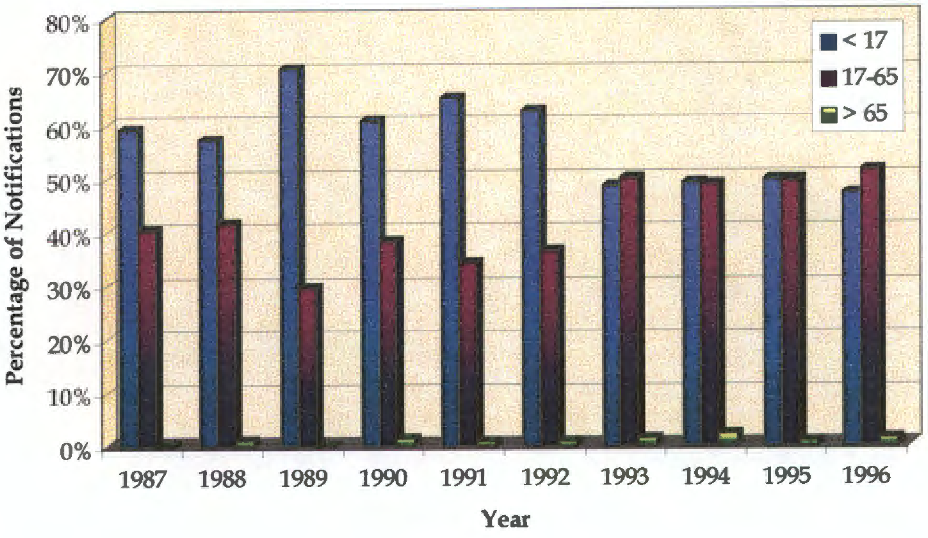


Figure 3.9. Differences in the distribution of malaria cases among age categories between 1987 and 1996. The proportion of notifications in the under-17 group was generally higher from 1987 to 1992, but from 1993 to 1996 the proportion was approximately equal. There seems to be no transitional step between the two extremes.

DEVELOPMENT OF THE MODEL

A model was developed to estimate the direct costs of first-line malaria treatment. At its core were the resistance variable, R, and the cost of the drug to the State. Other relevant costs, such as staff time, transport, maintenance, utilities and consumables were included, although R ultimately governed all to an extent.

4.1. Derivation of the Resistance Variable (R)

The resistance variable, R, describes the proportion of patients initially treated for malaria that return to the public health system for treatment if first line therapy fails. R is unique for every drug included in the study, and is a reflection of the effect resistance has on costs. It is defined as the product of P_R, the in vivo prevalence of drug resistance, and $P_P \pm 0.15$, the proportion of patients not cured by the first line drug that return to a clinic for further treatment. Please note that after sections 4.1.1 and 4.1.2, R will be represented by 2 decimal places only; calculated figures in tables may therefore appear to be slightly inaccurate, due to the use of the full 4 decimal places in spreadsheet calculations.

R is expressed by equation (1), as derived in section 2.5.3.1.

4.1.1. Chloroquine

$$R_{CQ} = 0.4792 \times (0.7 \pm 0.15)$$

$$R_{CQ} = 0.3354 \pm 0.0719$$

P_R for chloroquine is 47.92%, extrapolated from data collected during the recent *in vivo* study of chloroquine resistance conducted in Mpumalanga by the Department of Health and Welfare and the SA Medical Research Council's National Malaria Control Programme. P_P is an estimate (70%), considered appropriate by public health care professionals working in the district (personal communication, S Donahue, Shongwe Hospital).

4.1.2. *Sulfadoxine-pyrimethamine*

$$R_{SP} = 0.0550 \times (0.7 \pm 0.15)$$
$$R_{SP} = 0.0385 \pm 0.0083$$

P_R for sulfadoxine-pyrimethamine is 5.50%, and represents the total proportion of RI, RII and RIII[1] patients participating in the 1998 *in vivo* study of sulfadoxine-pyrimethamine resistance in Mpumalanga (Govere *et al*, in press).

4.2. Variable Costs

4.2.1. *Drug Costs*

4.2.1.1. *Chloroquine*

Adult	**Paediatric**
1.5g over 3 days: ♦ 600mg upon presentation ♦ 300mg 6-8 hours later ♦ 300mg after 24 hours ♦ 300mg after 48 hours	25 mg/kg over 3 days: ♦ 10 mg/kg upon presentation (up to maximum of 600mg) ♦ 5 mg/kg (up to 300mg) repeated 6, 24 and 48 hours after initial dose.

Table 4.1. Chloroquine dosage regimen for the first-line treatment of malaria.

Category	Total Dosage (mg)	Cost per 150mg Tablet (ZAR) (December 1997)	Total Cost per Treatment Course (ZAR/US$)
Adult >65 kg	1800	0.08	0.99/0.22
Adult	1500	0.08	0.83/0.18
Child 13-16 yrs	1050	0.08	0.58/0.13
Child 10-12 yrs	750	0.08	0.41/0.09
Child 4-9 yrs	600	0.08	0.33/0.07
Child <4 yrs*	375	0.08	0.21/0.04

Table 4.2. Cost per chloroquine treatment course. *Children under 4 years of age were assumed to have a mean weight of 15kg. Other figures are based upon district treatment protocols. Costs supplied by S Swanepoel, pharmacist at Shongwe Hospital. ZAR 1.00 was equivalent to a mean of US$ 0.217in 1997.

Category	Total Malaria Patients Treated at Naas Clinic in 1997	Cost per Treatment Course (ZAR)	Total Cost of Category (ZAR)
Adult >65	1	0.99	0.99
Adult 17-65	108	0.83	89.21
Child 13-16	51	0.58	29.49
Child 10-12	32	0.41	13.22
Child 4-9	39	0.33	12.89
Child <4	5	0.21	1.03
Total	236		146.82

Table 4.3. Total 1997 projected cost of chloroquine at Naas Clinic. ZAR 1.00 = US$ 0.217.

Category	Total Malaria Patients Treated at Mangweni Clinic in 1997	Cost per Treatment Course (ZAR)	Total Cost of Category (ZAR)
Adult >65	4	0.99	3.96
Adult 17-65	127	0.83	104.90
Child 13-16	45	0.58	26.02
Child 10-12	29	0.41	11.98

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[1] RI, RII and RIII resistance categories were originally developed for use in the amino-4-quinolines, but they are commonly used by the South African Department of Health as indicators of resistance in other antimalarial drug families.

Child 4-9	51	0.33	16.85
Child <4	15	0.21	3.10
Total	271		166.81

Table 4.4. Total 1997 projected cost of chloroquine at Mangweni Clinic. ZAR 1.00 = US$ 0.217.

4.2.1.2. *Sulfadoxine-pyrimethamine*

Adult	Paediatric
1500mg sulfadoxine + 75mg pyrimethamine as a single dose*	◆ < 1 yr: 125mg sulfadoxine + 6.25mg pyrimethamine single dose ◆ 1-3 yrs: 250mg sulfadoxine + 12.5mg pyrimethamine single dose ◆ 4-8 yrs: 500mg sulfadoxine + 25mg pyrimethamine single dose ◆ 9-14 yrs: 1000mg sulfadoxine + 50mg pyrimethamine single dose

Table 4.5. Sulfadoxine-pyrimethamine dosage regimen for the first-line treatment of malaria. *Doses have recently been revised to address underdosing issues; the doses above reflect these changes.

Category	Total Malaria Patients Treated at Naas Clinic in 1997	Cost per Treatment Course (ZAR/*US$*)	Total Cost of Category (ZAR)
Adult >14	143	18.50/*4.02*	2 645.50
Child 9-14	56	12.33/*2.68*	690.67
Child 4-8	32	6.17/*1.34*	197.33
Child 1-3	3	3.08/*0.67*	9.25
Child <1	2	1.54/*0.33*	3.08
Total	236		3 545.83

Table 4.6. Total 1997 projected cost of sulfadoxine-pyrimethamine at Naas Clinic. ZAR 1.00 = US$ 0.217.

Category	Total Malaria Patients Treated at Mangweni Clinic in 1997	Cost per Treatment Course (ZAR)	Total Cost of Category (ZAR)
Adult >14	156	18.50	2 886.00
Child 9-14	58	12.33	715.33
Child 4-8	42	6.17	259.00
Child 1-3	14	3.08	43.17
Child <1	1	1.54	1.54
Total	271		3 903.04

Table 4.7. Total 1997 projected cost of sulfadoxine-pyrimethamine at Mangweni Clinic. ZAR 1.00 = US$ 0.217.

4.2.1.3. Quinine

According to standard operating procedure in the public health system in the Shongwe and Tonga districts of Mpumalanga, patients who have not responded adequately to first-line drug therapy (typically, those who present a few days later and show no improvement) are referred to Shongwe Hospital. Once there, they are admitted, either to receive intravenous quinine treatment or to ensure compliance with oral quinine. The average length of a hospital stay was 3 days, and it was estimated that it was necessary to treat 70% of clinic-referred malaria patients with IV quinine for the duration of their stay (S Donahue, Shongwe Hospital).

Adult & Paediatric	
Loading dose:	Quinine dihydrochloride 20mg/kg by IV infusion, over 4 hours in 5% dextrose saline. No loading dose to be given if patient has taken mefloquine, quinine or halofantrine in preceding 24 hours. It was assumed that this situation did not apply to any of the study patients.
Maintenance dose:	Quinine hydrochloride 10mg/kg by IV infusion, over 4 hours in 5% dextrose saline, starting 8 hours after loading dose and repeated 8 hourly until patient is able to tolerate quinine administered orally.

Table 4.8. Intravenous quinine dosage regimen for the treatment of severe and/or complicated malaria (Smith *et al*, 1997; White, 1996).

Adult	Paediatric
Quinine sulphate 600mg 8-hourly for 7 days	Quinine sulphate 10mg/kg body weight 8-hourly for 7 days

Table 4.9. Oral quinine dosage regimen for the treatment of non-severe malaria resistant to first-line treatment (Smith *et al*, 1997).

Description	Cost (ZAR, 1997)
Quinine sulphate IV, 300mg per 10ml ampoule	5.43 per ampoule (US$ 1.78)
Quinine dihydrochloride, 300mg per tablet	0.91 per tablet (US$ 0.20)

Table 4.10 . Quinine drug costs in 1997. (Prices observed at Shongwe Hospital pharmacy.) ZAR 1.00 = US$ 0.217 in 1997.

The weight of each malaria notification was estimated from the patient's age using NCHS Growth Charts (National Center for Health Statistics, 1976). Quinine dosage, and hence cost of therapy, was estimated from weight. The results appear in Fig. 4.2 (p 61).

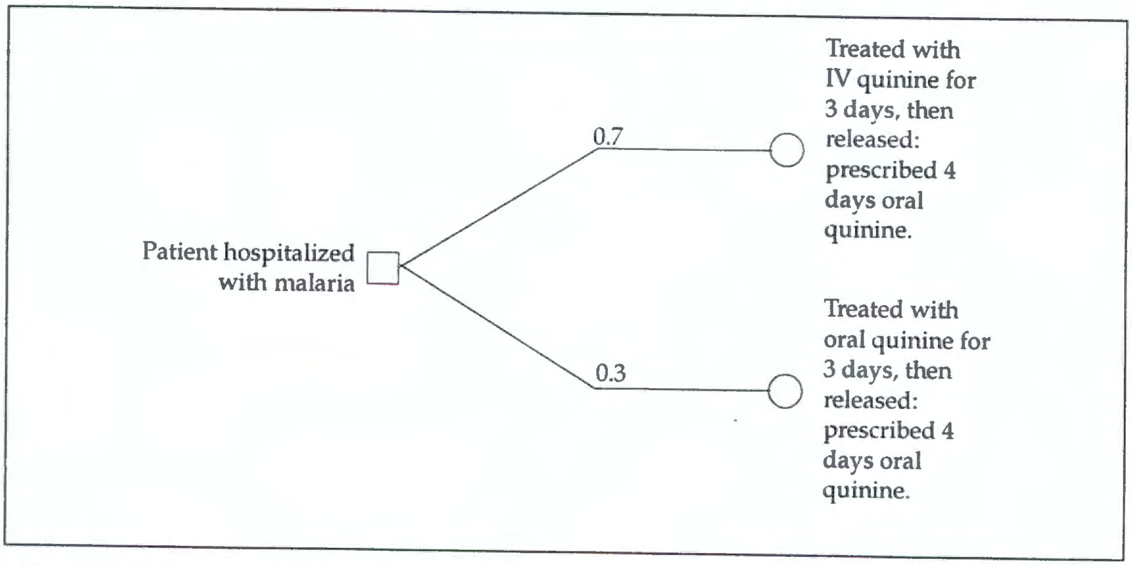

Figure 4.1. Typical decision tree for patients referred to Shongwe Hospital from clinics with resistant malaria. 70% ± 15% of admitted referrals are sufficiently severe to warrant treatment with a 3 day course of intravenous quinine, whereas the remaining 30% ± 15% receive oral quinine and remain under observation for 3 days. Upon release, both IV and PO patients receive a prescription for a further 4 days of oral quinine (estimates of proportion provided by S Donohue, Shongwe Hospital).

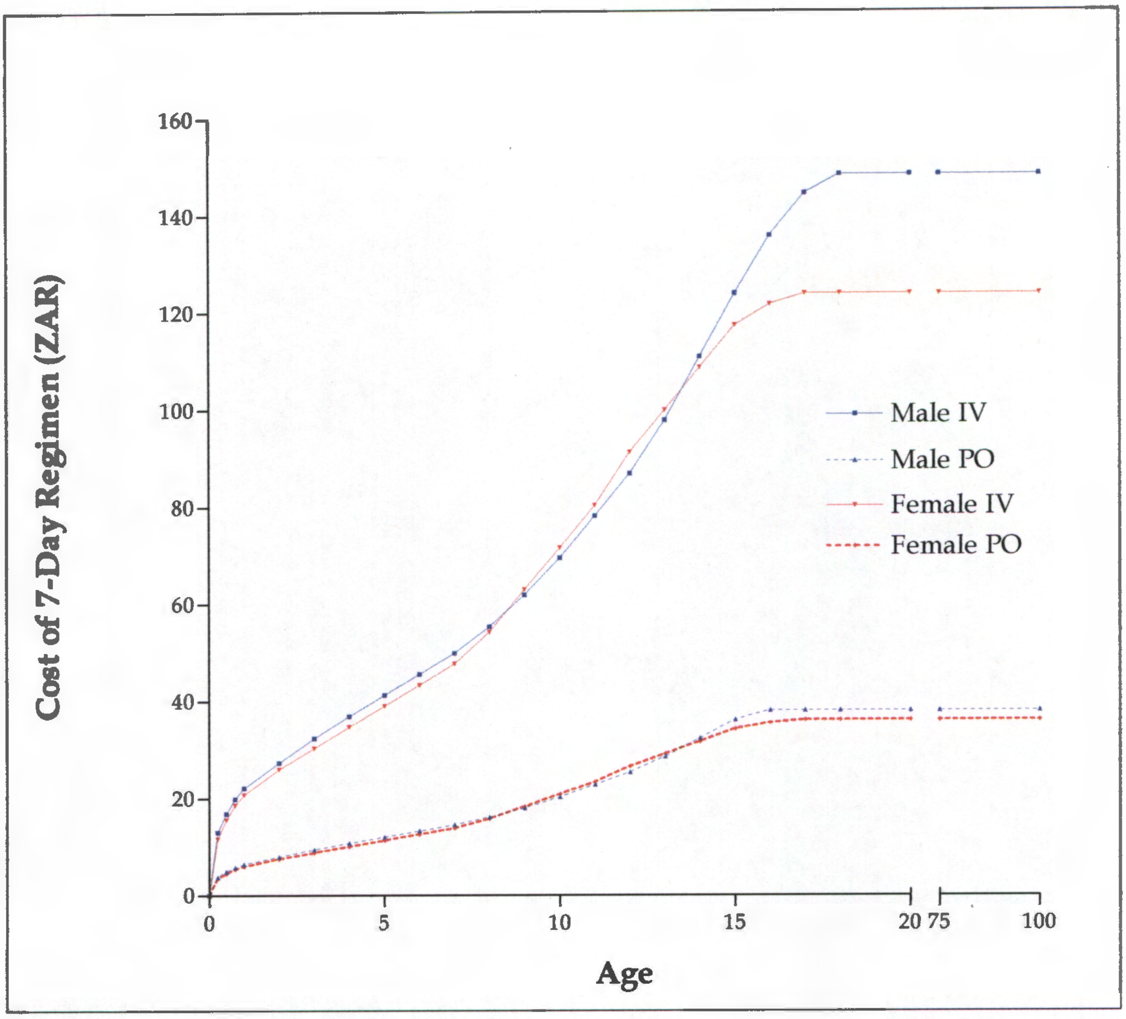

Figure 4.2. Differences in cost of intravenous and oral quinine therapy, by age, in the Tonga District of Mpumalanga in 1997. Age/weight relationships are estimated from NCHS Growth Charts (National Center for Health Statistics, 1976). Differences in gender were factored into the calculations. ZAR 1.00 = US$ 0.217 in 1997.

The formula for calculating first-line drug cost for each age group is represented by equation 3 (p 33). Cumulative drug costs may be calculated by adding $Cost_Q$ (equation (6), p 34) to $Cost_{Da}$, yielding $Cost_{Di}$ for drug *i*.

For example, a female patient aged 7 years would weigh 22kg, according to the NCHS charts. If the case were severe, an IV course would be used. A loading dose of IV quinine for this patient would cost 22 x 20 x R0.018, or R7.96. After the loading dose, using the default IV course over 3 days, 8 doses of 10 mg/kg would be administered, a total cost of 8 x 22 x 10 x R0.018, or R31.44. After the 3 days of intravenous therapy, a further 4 days of oral therapy is administered: 12 x 22 x 10 x R0.003, or R7.94. Adding the loading dose, the remainder of the intravenous quinine course, and the oral quinine course, the total cost for this patient would be R47.34.

If she were admitted with mild, but resistant, malaria, she would be treated orally for 7 days: the cost would be 21 x 22 x 10 x R0.003, or R13.94.

The cost of both IV and PO quinine therapy was calculated for each patient, and totalled for each clinic. The total was then divided by the number of malaria notifications at each clinic, to yield the cost-per-patient of IV and PO quinine therapy at Naas (R112.10 and R30.50, respectively) and Mangweni (R108.95 and R29.66, respectively).

Chloroquine

Clinic	No. of patients in 1997	*R*	Est. no. of referrals	Cost to treat with IV Quinine (ZAR)		Cost to treat with PO Quinine (ZAR)	
				Per patient	Adj. (Referrals x 0.7 ± 0.15)	Per patient	Adj. (Referrals x 0.3 ± 0.15)
Naas	236	0.3354 ± 0.07188	79.15 ± 16.96	112.10	6 211.25 ± 2 947.37	30.50	724.26 ± 594.96
						Total for Naas (IV + PO)	6 935.51 ± 3542.32
Mangweni	271	0.3354 ± 0.07188	90.89 ± 19.48	108.95	6 931.99 ± 3 289.37	29.66	808.77 ± 664.38
						Total for Mangweni (IV + PO)	7 740.76 ± 3953.75

Table 4.11. Calculation of quinine costs per clinic, assuming first-line drug is chloroquine (R=0.3354 ± 0.07188). Quinine costs are dependent on the number of referred patients, hence the resistance variable R, and hence drug. ZAR 1.00 = US$ 0.217.

Sulfadoxine-pyrimethamine

Clinic	No. of patients in 1997	*R*	Est. no. of referrals	Cost to treat with IV Quinine (ZAR)		Cost to treat with PO Quinine (ZAR)	
				Per patient	Adj. (Referrals x 0.7 ± 0.15)	Per patient	Adj. (Referrals x 0.3 ± 0.15)
Naas	236	0.0385 ± 0.0083	9.09 ± 1.96	112.10	712.98 ± 339.43	30.50	83.14 ± 68.45
						Total for Naas (IV + PO)	796.12 ± 407.88
Mangweni	271	0.0385 ± 0.0083	10.43 ± 2.25	108.95	795.71 ± 378.81	29.66	92.84 ± 76.44
						Total for Mangweni (IV + PO)	888.55 ± 455.25

Table 4.12. Calculation of quinine costs per clinic, assuming first-line drug is sulfadoxine-pyrimethamine (R=0.0385 ± 0.0083). ZAR 1.00 = US$ 0.217.

Summary

Study Clinic	Chloroquine Cost (ZAR)			Sulfadoxine-pyrimethamine (ZAR)		
	CQ Cost (Clinic Cost)	Quinine Cost (Hospital Cost)	Total Cost	SP Cost (Clinic Cost)	Quinine Cost (Hospital Cost)	Total Cost
Naas	145.79	6 935.51 ± 3542.32	7 081.30 ± 3542.32	3 545.83	796.12 ± 407.88	4 341.95 ± 407.88
Mangweni	163.71	7 740.76 ± 3953.75	7 904.47 ± 3953.75	3 903.04	888.55 ± 455.25	4 791.59 ± 455.25

Table 4.13. Total projected 1997 drug costs for the treatment of patients originating at the study clinics. ZAR 1.00 = US$ 0.217.

Clinic	Total Drugs Cost (Per Patient) of Malaria in 1997 (ZAR)		Difference in Cost per Patient (ZAR)
	Chloroquine	Sulfadoxine-Pyrimethamine	
Naas	30.01 ± 15.01	18.40 ± 1.73	11.61 ± 13.28
Mangweni	28.56 ± 14.59	17.68 ± 1.68	11.49 ± 12.91
Mean	**29.29 ± 14.80**	**18.04 ± 1.71**	**11.55 ± 13.10**

Table 4.14. Summary of drug costs of malaria cases originating at Naas (236 cases) and Mangweni (271 cases) Clinics in 1997, using chloroquine and sulfadoxine-pyrimethamine as first-line agents. ZAR 1.00 = US$ 0.217.

Simulation Results

Clinic	Total Drugs Cost (Per Patient) of Malaria in 1997 ($\mu \pm \sigma$/ZAR)	
	Chloroquine	Sulfadoxine-Pyrimethamine
Naas	31.12 ± 10.57	18.48 ± 1.25
Mangweni	29.96 ± 10.65	17.80 ± 1.17
Mean	**30.54 ± 10.61**	**18.14 ± 1.21**

Table 4.15. Results of the Monte Carlo simulation for drug costs. ZAR 1.00 = US$ 0.217.

4.2.2. *Clinical Staff Costs*

4.2.2.1. *Clinical Staff Makeup and Salaries*

Naas Clinic

Naas employs a total of 22 clinical employees, as detailed in Table 2, accounting for a total annual clinical staff cost (as at 1997) of R 1 107 191.40 (US$ 240 317.33). At present there is one vacant Emergency Care Practitioner post, which has been frozen. A more detailed description of these data is presented in Appendix 1.

Position Category	Number of staff (Q_i)	Monthly wage or salary (ZAR) (W_i)	Annual fringe benefits (ZAR) (FB_i)	Total annual cost of position including benefits (ZAR) $((Q_i \times [(T_i \times W_i) + FB_i]))$
Prof. nurse	11	3 709.50	17 805.60	685 515.60
Staff nurse	1	2 533.00	12 158.40	42 554.40
Emerg. care practitioner	3 (1 vacancy)	2 533.00	12 158.40	127 663.20
Nursing assts	7	2 138.55	10 263.60	251 458.20
Total	22			1 107 191.40

Table 4.16. Total salaries and benefits paid to nursing staff at the clinic at Naas in 1997, as well as numbers of staff per job category. ZAR 1.00 = US$ 0.217.

Mangweni Clinic

Mangweni Clinic maintains a permanent clinical staff of 23, with no vacancies at present. Total clinical staff cost amounted to ZAR 1 149 745.80 (US$ 249 554.13) in 1997. A description of this information appears as Table 4.17, and a more detailed summary of the data is contained in Appendix 1.

Position Category	Number of staff (Q_i)	Monthly wage or salary (ZAR) (W_i)	Annual fringe benefits (ZAR) (FB_i)	Total annual cost of position including benefits (ZAR) $((Q_i \times [(T_i \times W_i) + FB_i]))$
Prof. nurse	11	3 709.50	17 805.60	685 515.60
Staff nurse	1	2 533.00	12 158.40	42 554.40
Emerg. care practitioner	4	2 533.00	12 158.40	127 663.20
Nursing assts	7	2 138.55	10 263.60	251 458.20
Total	23			1 149 745.80

Table 4.17. Total salaries and benefits paid to clinical staff at the clinic at Mangweni in 1997, as well as numbers of staff per job description. ZAR 1.00 = US$ 0.217.

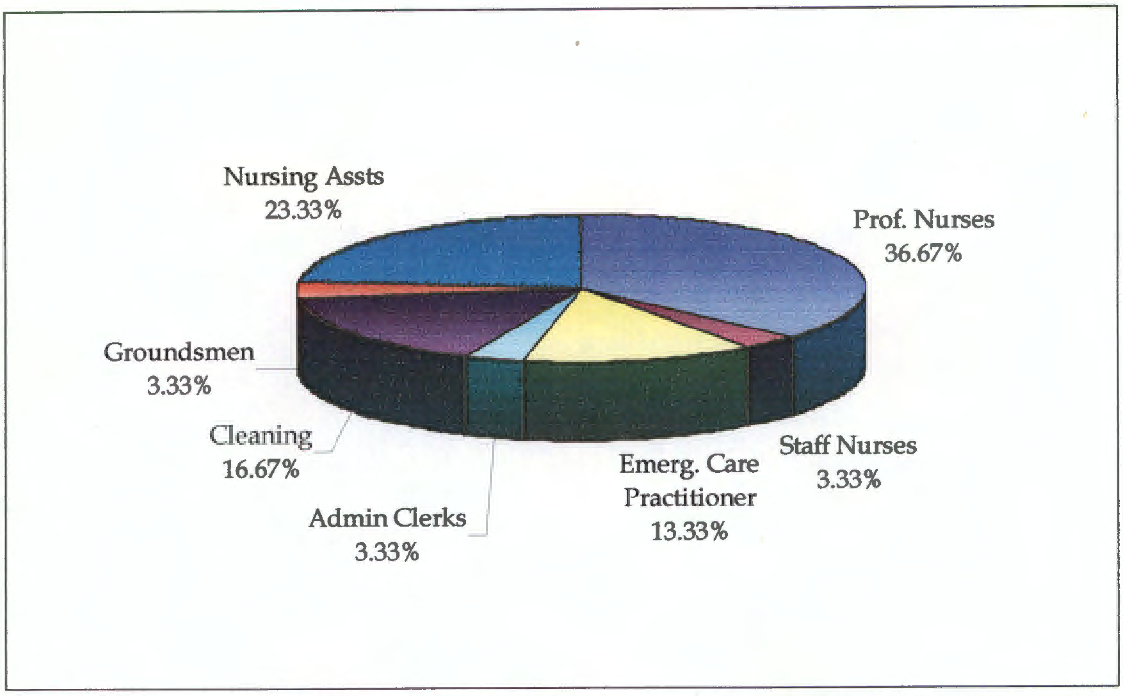

Figure 4.3. Proportional breakdown of job types at Naas and Mangweni Clinics, as percentages of the total staff complement, assuming all posts are filled.

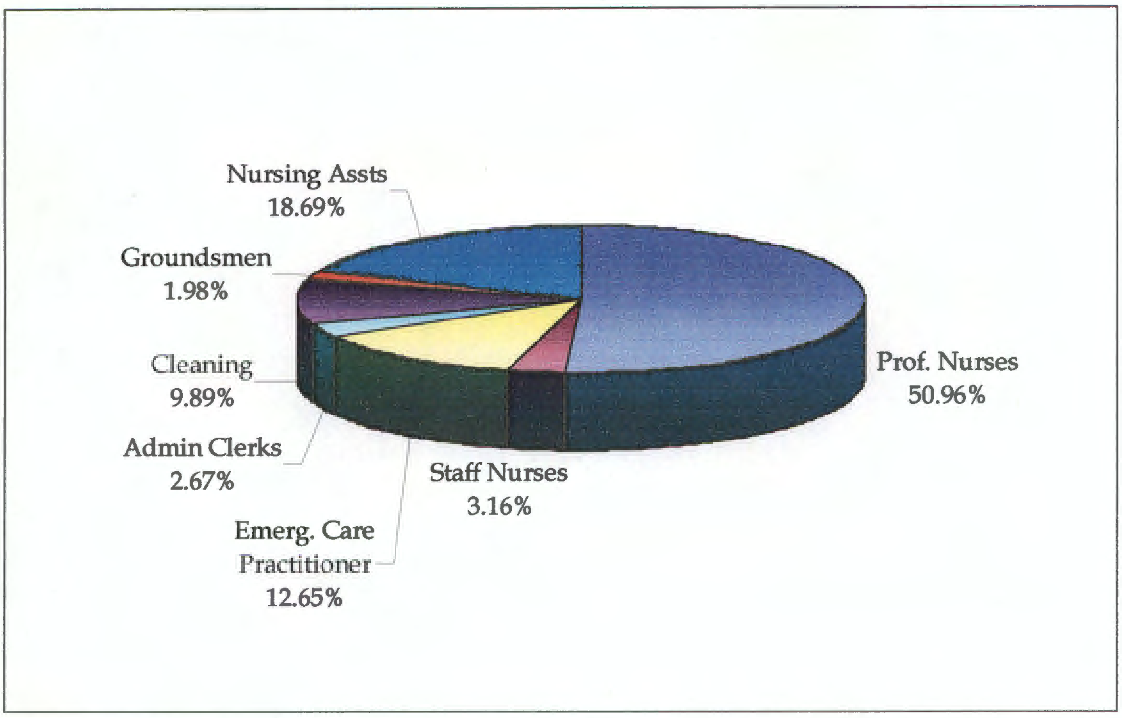

Figure 4.4. Proportional breakdown of salaries by job type at Naas and Mangweni Clinics, assuming all posts are filled. ZAR 1.00 = US$ 0.217.

The largest category of staff employed at Shongwe Hospital is nursing (278, 43.2%), and a similar proportion of the annual staff cost at the hospital (ZAR 12 890 043.60, US$ 2 797 804.22, 46.9%) is attributable to nurses. Descriptions of the other categories appear as Table 1, as well as Figure 4.5 and Figure 4.6. A detailed description of the staff and salary makeup of the hospital appears as Appendix A.

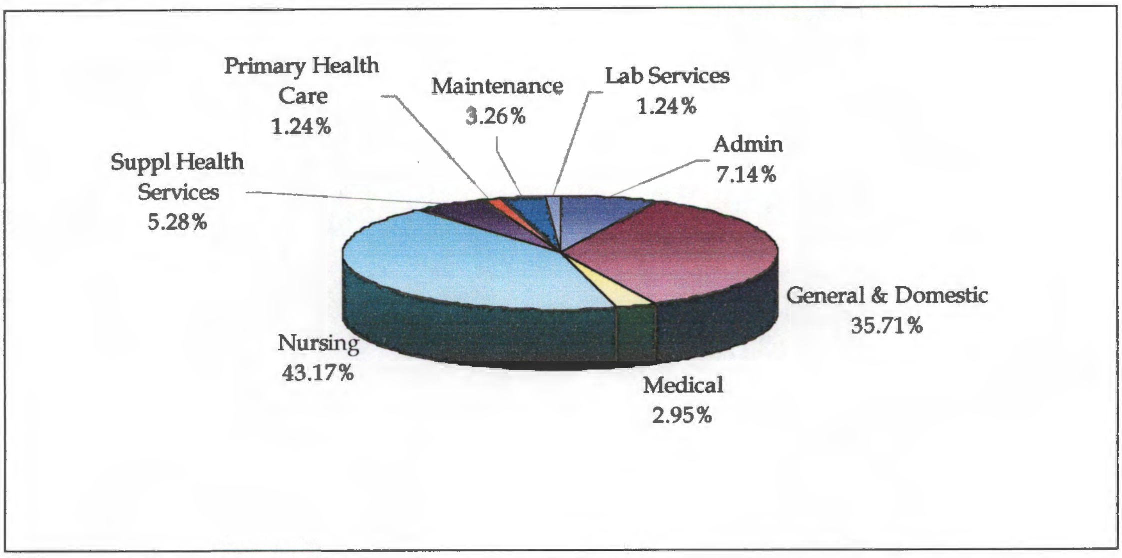

Figure 4.5. Proportional breakdown of job types at Shongwe Hospital, as percentages of the total staff complement.

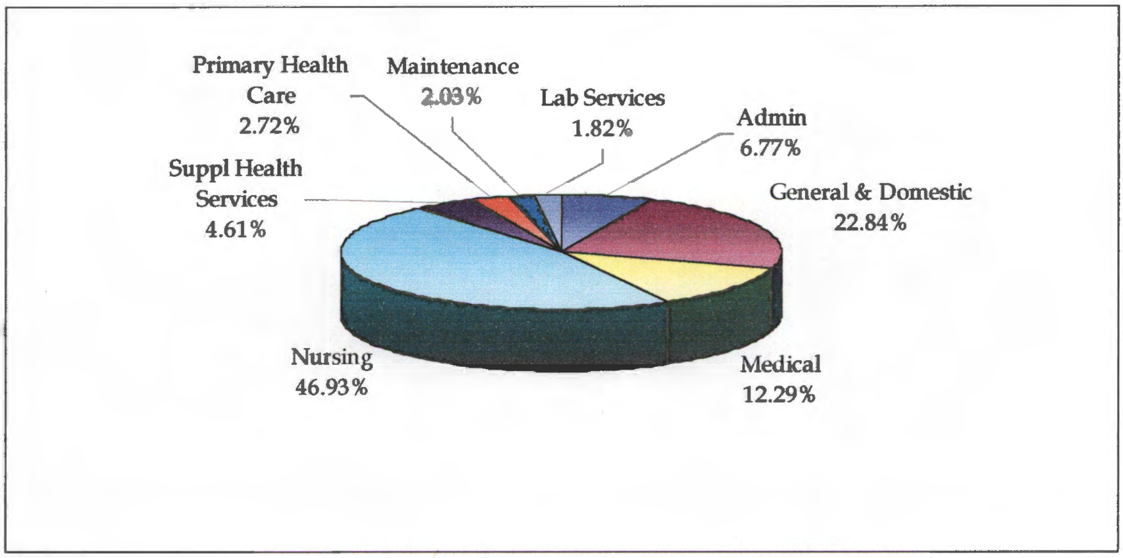

Figure 4.6. Proportional breakdown of salaries by job type at Shongwe Hospital. ZAR 1.00 = US$ 0.217.

.Position Category	Number of staff (Q_i)	Monthly wage or salary (ZAR) (W_i)	Annual fringe benefits (ZAR) (FB_i)	Total annual cost of position including benefits (ZAR) $((Q_i \times [(T_i \times W_i) + FB_i]))$
Medical	19	See Appendix A	See Appendix A	3 374 232.24
Nursing	278			12 890 043.60
Suppl Health Services	34			1 265 048.40
Primary Health Care	8			747 066.24
Total	**644**			**18 276 390.48**

Table 4.18. Total salaries and benefits paid to clinical staff at Shongwe Hospital in 1997, as well as numbers of staff per category. Subcategories and details of wages and benefits appear in Appendix A.

4.2.2.2. *Calculation of costs*

Equations 7, 8 and 9 (pp 34-5) were used for the calculation of costs.

Naas & Mangweni Clinics

Since three categories of nursing staff are employed by the clinics – professional nurses, staff nurses and nursing assistants, all with differing salaries, with interchangeable duties -- it was necessary to calculate a mean salary. Average salary, including benefits, among the 19 staff belonging to these three categories was R51 544.12 (US$ 11 187.73) per annum. Emergency care practitioners, although clinical staff, were omitted since malaria cases rarely, if ever, require this kind of attention, regardless of the severity of their condition.

All malaria notifications originating at the clinic are assumed to have been consultations. The number of returning patients is estimated by *R*; each returning patient is assumed to need another consultation. Consultations for malaria by nursing staff at both clinics were observed to take an average of ten minutes, during which a brief history would be taken, and an ICT used for diagnosis.

Nursing staff work 40 hours a week, with 45 days' leave per annum, giving a total of 109 371.43 minutes worked per annum. Therefore, the salary of an average nursing staff member would be R0.47/min, or US$ 0.10/min (D Nkosi, Shongwe District Manager, Department of Health and Welfare, Mpumalanga). This figure makes provision for leave.

Chloroquine

Clinic	Resistance Variable (1 + *R*)	Adjusted Number of Malaria Patients (n_{mi} x (1 + *R*))	Time per Consultation ($Time_{ci}$) (min)	Mean Salary per Minute (S_{mi}) (ZAR/min)	Total Clinical Staff Cost ($Cost_{CSi}$) (ZAR)	Clinical Staff Cost per Notified Patient ($Cost_{CSi}/n_{mi}$) (ZAR)
Naas	1.34 ± 0.072	315.15	10	0.47	1 485.25 ± 79.95	6.29 ± 0.25
Mangweni	1.34 ± 0.072	361.89	10	0.47	1 705.52 ± 91.80	6.29 ± 0.25

Table 4.19. Clinical staff costs at Naas & Mangweni Clinics for chloroquine in 1997. All posts were assumed to be filled. ZAR 1.00 = US$ 0.217.

Sulfadoxine-pyrimethamine

Clinic	Resistance Variable (1 + *R*)	Adjusted Number of Malaria Patients (n_{mi} x (1 + *R*))	Time per Consultation ($Time_{ci}$) (min)	Mean Salary per Minute (S_{mi}) (ZAR/min)	Total Clinical Staff Cost ($Cost_{CSi}$) (ZAR)	Clinical Staff Cost per Notified Patient ($Cost_{CSi}/n_{mi}$) (ZAR)
Naas	1.04 ± 0.0083	245.09 ± 1.96	10	0.47	1 155.03 ± 9.23	4.89 ± 0.04
Mangweni	1.04 ± 0.0083	281.43 ± 2.25	10	0.47	1 326.33 ± 10.60	4.89 ± 0.04

Table 4.20. Clinical staff costs at Naas & Mangweni Clinics in 1997, assuming first-line therapy was sulfadoxine-pyrimethamine. All posts were assumed to be filled. ZAR 1.00 = US$ 0.217.

Referred patients at Shongwe Hospital would be seen by two types of clinical staff: nursing staff, at least once, who would attend to such matters as intravenous infusions, and medical staff, who would see them daily (during the routine ward round).

Mean annual salary including benefits for the 18 frontline medical staff was R170 534.46 (US$ 37 014.77) per annum, including benefits. This included interns, specialist physicians, etc, all of whom were classified and paid as Medical Officers. The hospital superintendent was not included in the assessment of costs, because his position entailed no patient contact. Mean annual salary including benefits for the 278 nurses was R46 367.06 (US$ 10 064.04). The same shifts were assumed to apply.

Medical staff worked an average of 50 hours per week with 45 days' leave per annum. Therefore, each staff member worked 137 250 minutes on site per annum, resulting in a total salary of R1.24 (US$ 0.27) per minute. Medical and nursing staff time were the only cadres taken into account.

Expert interviews were conducted with a number of health professionals at various malaria-endemic sites around the country to assess the amount of staff time spent on each of the two types of admitted patient. The results are summarised in Table 20 below.

Type	Medical	Nursing
Moderately severe (3 days of oral quinine, followed by release)	5 minutes per 24 hours, during ward round; 25 minutes on admission (45 min total over 3 days)	60 minutes per 24 hours (180 min total for 3 days)
Severe and/or complicated	25 minutes per 24 hours; 30 minutes on admission (105 min total over 3 days)	180 minutes per 24 hours (540 min total for 3 days)

Table 4.21. Estimates of time spent daily by clinical staff on hospitalised malaria patients. (Compiled from expert interviews with Dr S Donohue, Shongwe Hospital, Mpumalanga; Dr H Born-Williams & K Dlamini, Mosveld Hospital, KwaZulu-Natal; Dr H McIlleron, Department of Pharmacology, University of Cape Town.)

Chloroquine

Clinic of Origin	Resistance Variable (R)	Patients admitted for IV Quinine (R_{IV} x Rn_{mi})	Patients admitted for Oral Quinine ((1-R_{IV}) x Rn_{mi})	Cost of Medical Staff Time (ZAR)	Cost of Nursing Staff Time (ZAR)	Total Cost of Clinical Staff Time (ZAR)
Naas	0.3354 ± 0.07188	55.41 ± 19.51	23.75 ± 19.51	8 556.46 ± 3 635.88	16 115.14 ± 6 619.51	24 671.60 ± 10 255.38
Mangweni	0.3354 ± 0.07188	63.63 ± 22.40	27.27 ± 22.40	9 825.43 ± 4 175.09	18 505.10 ± 7 601.21	28 330.50 ± 11 736.31

Table 4.22. Estimated clinical staff costs at Shongwe Hospital for chloroquine in 1997. ZAR 1.00 = US$ 0.217.

Sulfadoxine-pyrimethamine

Clinic of Origin	Resistance Variable (R)	Patients admitted for IV Quinine (R_{IV} x Rn_{mi})	Patients admitted for Oral Quinine ((1-R_{IV}) x Rn_{mi})	Cost of Medical Staff Time (ZAR)	Cost of Nursing Staff Time (ZAR)	Total Cost of Clinical Staff Time (ZAR)
Naas	0.0385 ± 0.0083	6.36 ± 2.25	2.73 ± 2.25	982.18 ± 419.84	1 849.43 ± 764.36	2 832.01 ± 1 184.19
Mangweni	0.0385 ± 0.0083	7.30 ± 2.59	3.13 ± 2.59	1 127.84 ± 482.10	2 124.17 ± 877.71	3 252.01 ± 1 359.81

Table 4.23. Clinical staff costs at Naas & Mangweni Clinics in 1997, assuming first-line therapy was sulfadoxine-pyrimethamine. ZAR 1.00 = US$ 0.217.

Summary

Clinic	Total Clinical Staff Cost (ZAR)	
	Chloroquine	Sulfadoxine-pyrimethamine
Naas	26 156.85 ± 10 335.33	3 987.04 ± 1 193.42
Mangweni	30 036.04 ± 11 868.11	4 578.34 ± 1 370.41

Table 4.24. Total clinical staff costs of malaria notifications originating at the study clinics. ZAR 1.00 = US$ 0.217.

Clinic	Total Clinical Staff Cost (Per Patient) of Malaria in 1997 (ZAR)		Difference in Cost per Patient (ZAR)
	Chloroquine	Sulfadoxine-Pyrimethamine	
Naas	110.83 ± 43.79	16.89 ± 5.06	93.94 ± 38.74
Mangweni	110.83 ± 43.79	16.89 ± 5.06	93.94 ± 38.74
Mean	**110.83 ± 43.79**	**16.89 ± 5.06**	**93.94 ± 38.74**

Table 4.25. Summary of clinical staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and sulfadoxine-pyrimethamine as first-line agents. ZAR 1.00 = US$ 0.217.

Simulation Results

Clinic	Total Clinical Staff Cost (Per Patient) of Malaria in 1997 (μ ± σ/ZAR)	
	Chloroquine	Sulfadoxine-Pyrimethamine
Naas	112.09 ± 26.44	16.89 ± 3.19
Mangweni	110.45 ± 27.19	16.92 ± 3.00
Mean	**111.27 ± 26.82**	**16.91 ± 3.10**

Table 4.26. Results of the Monte Carlo simulation for clinical staff costs. ZAR 1.00 = US$ 0.217.

4.2.3. *Consumables*

The consumables cost equation 10 (p 35) was used for the calculation of costs.

4.2.3.1. *Naas & Mangweni Clinics (First-line treatment)*

Item	Unit Cost (ZAR)
ICT Malaria P.f. Kits	0.80*
Cotton Wool Swabs	0.02
Lancets	0.04
Alcohol Swabs	0.05
Non-Sterile Pairs of Gloves	0.17
Total Consumables Cost per First-Line Malaria Test (C_f)	**1.08 (US$ 0.23)**

Table 4.27. The costs of consumables used in first-line malaria treatment at clinic level. * Figure obtained from R+R Marketing, South African distributors for ICT. ZAR 1.00 = US$ 0.217.

The malaria blood smear positivity rate at the Shongwe Hospital laboratory for Naas and Mangweni Clinics was used in the estimation of the number of patients tested for malaria at these sites in 1997.

Clinic	1997 Notifications	1991-1996 Positivity Rate (R_p)	Estimated Malaria Tests in 1997	Total cost of malaria testing in 1997 (ZAR)	Cost per Notified Patient in 1997 (ZAR)
Naas	236	7.45%	3 168	3 405.60	14.43
Mangweni	271	4.78%	5 669	6 094.18	22.49

Table 4.28. Total consumables costs of malaria testing at Naas and Mangweni Clinics in 1997. ZAR 1.00 = US$ 0.217.

4.2.3.2. *Shongwe Hospital (referred patients)*

Referred patients make use of a much wider range of consumables at Shongwe Hospital, although this is dependent on the prevalence of resistance to the modelled drug. These items include IV kits, saline, glucose and dextrose drips, and other items of this type. A standard list of consumables used by a typical severe and/or complicated case of malaria was prepared to assess costs.

Item	Quantity (Q_i)	Unit Cost (P_i) (ZAR)	Total Cost (C_{IV3}) (ZAR)
IV Set	1	2.02	2.02
Cannula needle	1	1.41	1.41
Cannula tape (Webcol)	1	0.05	0.05
Cotton swab (1g)	1	0.02	0.02
Dextrose NaCl (500ml)	9	7.92	71.28
Meals (3 per day)	3 days	30.19	90.57
Total consumables cost per 3-day IV quinine course (C_{IV3})			**165.35 (US$ 35.88)**

Table 4.29. Consumables cost per patient receiving a standard 3-day course of IV quinine at hospital level, based on observed consumables use in individual hospital malaria patients. Costs of meals implicitly included staff meals, since costs were calculated as a proportion of the hospital's annual meals budget. Laboratory costs were generally not incurred, and so have been omitted. ZAR 1.00 = US$ 0.217.

4.2.3.3. *Calculation of Consumables Costs*

Naas Clinic

From equation 10 (p 35), assuming the use of chloroquine as first-line agent, we have:

$$Cost_C = (3168\times1.075)+\{(79.15\pm16.96)\times[(0.7\pm0.15)\times(74.774+1.075)]+[(0.3\pm0.15)\times1.075]\}$$
$$\therefore Cost_C = 7633.54\pm1999.72)$$

where $n_{mi} = 236$, $R_p = 0.0745$, $C_f = 1.075$, $Rn_{mi} = 79.15 \pm 16.96$, $R_{IV} = 0.7 \pm 0.15$, and $C_{IV3} = 165.34$.

The estimated total cost of consumables used in the treatment of malaria cases originating at Naas Clinic, assuming use of chloroquine as first-line agent, was R12 651.63 ± R4 380.90 (US$ 2 745.40 ± US$ 950.66) in 1997.

Substituting sulfadoxine-pyrimethamine for chloroquine (involving a change in the resistance variable *R*), the total consumables cost would be R4 466.73 ± R504.52 (US$ 969.28 ± US$ 109.48).

Mangweni Clinic

Similarly, the cost of consumables used in the treatment of malaria cases originating at Mangweni Clinic for each of the two first-line antimalarials was calculated as:

Drug	*Cost$_C$*
Chloroquine	R16 712.20 ± R5 030.61 *(US$ 3 626.55 ± US$ 1 091.64)*
Sulfadoxine-pyrimethamine	R7 313.43 ± R579.34 *(US$ 1 587.01 ± US$ 125.72)*

4.2.3.4. *Summary*

Clinic	Total Consumables Cost (Per Notified Patient) of Malaria in 1997 (ZAR)		Difference in Cost per Patient (ZAR)
	Chloroquine	**Sulfadoxine-Pyrimethamine**	
Naas	53.61 ± 18.56	18.93 ± 2.14	34.68 ± 16.42
Mangweni	61.67 ± 18.56	26.99 ± 2.14	34.68 ± 16.42
Mean	**57.64 ± 18.56**	**22.96 ± 2.14**	**34.68 ± 16.42**

Table 4.30. Summary of consumable costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and sulfadoxine-pyrimethamine as first-line agents. A mean 1997 exchange rate of R4.6072 to the US dollar was used.

Simulation Results

Clinic	Total Consumables Cost (Per Patient) of Malaria in 1997 ($\mu \pm \sigma$/ZAR)	
	Chloroquine	**Sulfadoxine-Pyrimethamine**
Naas	63.18 ± 11.20	19.96 ± 1.35
Mangweni	70.62 ± 11.60	28.05 ± 1.28
Mean	**66.90 ± 11.40**	**24.01 ± 1.32**

Table 4.31. Results of the Monte Carlo simulation for consumables costs. ZAR 1.00 = US$ 0.217.

4.2.4. *Transport*

While Shongwe Hospital itself has no vehicles assigned to ambulance duty, two were borrowed from other facilities for this purpose:

- a 1991 Isuzu KB pickup truck from Themba Hospital, valued at approximately R 21 000, with a fuel consumption of 10.7 litres per 100 km (estimated by Reeds Delta); and
- a 1988 Toyota Hiace minibus from Ermelo Hospital, with a fuel consumption of 13.3 litres per 100 km (estimated by Market Toyota).

The vehicles followed no set routine, but were dispatched to and from clinics as necessary. Both were no longer operational at the time of writing. The mean fuel price of 93% octane in 1997 was R 2.20 per litre in Mpumalanga (personal communication, J Smalberger, Shell Cape Town). Distance covered by the vehicles was dependent on the number of malaria cases referred by the clinics, which was in turn dependent on the *in vivo* resistance of *P. falciparum* to each particular drug.

Clinic	**Number of Vehicles (NV_i)**	**No of patients**	**Combined road distance per trip to clinic**	**Total Kilometres Covered for All Malaria Cases in 1997 (KM_i)**	**Operating Cost per Kilometre (C_i) (ZAR)**	$\sum_{i=1}^{i=n} TRC_i$
Naas	2	79.15 ± 16.96	80.0	6 332.35 ± 1357.09	0.264	1 671.74 ± 358.27
Mangweni	2	90.89 ± 19.48	77.0	6 998.79 ± 1499.92	0.264	1 847.68 ± 395.98

Table 4.32. Transport costs of first-line malaria treatment with chloroquine at Naas and Mangweni Clinics. Operating cost per kilometre was taken as the mean of the two vehicles' fuel consumption (12.0 l per 100 km). *KM_i* was calculated by multiplying the estimated number of recrudescent patients from each clinic by the total distance that would have to be covered by a vehicle travelling from Shongwe Hospital to the clinic and back again. It was assumed that each vehicle handled exactly 50% of the load, and that each patient was conveyed separately. ZAR 1.00 = US$ 0.217.

Clinic	Number of Vehicles (NV_i)	No of patients	Combined road distance per trip to clinic	Total Kilometres Covered for Malaria Cases in 1997 (KM_i)	Operating Cost per Kilometre (C_i) (ZAR)	$\sum_{i=1}^{i=n} TRC_i$
Naas	2	9.09 ± 1.96	80.0	726.88 ± 156.70	0.264	191.90 ± 41.37
Mangweni	2	10.43 ± 2.25	77.0	803.38 ± 173.20	0.264	212.09 ± 45.72

Table 4.33. Transport costs of first-line malaria treatment with sulfadoxine-pyrimethamine.

Clinic	Total Transport Cost (Per Patient) of Malaria in 1997 (ZAR)		Difference in Cost per Patient (ZAR)
	Chloroquine	Sulfadoxine-Pyrimethamine	
Naas	7.08 ± 1.52	0.81 ± 0.18	6.271 ± 1.343
Mangweni	6.82 ± 1.46	0.78 ± 0.17	6.035 ± 1.292
Mean	**6.95 ± 1.49**	0.80 ± 0.18	**6.153 ± 1.318**

Table 4.34. Summary of transport costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and sulfadoxine-pyrimethamine as first-line agents. ZAR 1.00 = US$ 0.217.

Since distance from the hospital is an important determinant of costs, and varies from clinic to clinic, a distance ratio, R_d, was derived from the Naas and Mangweni patient data.

$$Cost_{Tp} = R_d \times Dist_i \qquad (18)$$

R_d was calculated to be 0.0784, where $Cost_{Tp}$ is the total transport cost per patient at a specific clinic, and $Dist_i$ is the road distance covered by a vehicle travelling from the hospital to the clinic and back again.

This allows the difference in 1997 transport costs per patient to be calculated for any clinic within the district for a given drug.

Clinic	Total Transport Cost (Per Patient) of Malaria in 1997 ($\mu \pm \sigma$/ZAR)			
	Chloroquine		Sulfadoxine-Pyrimethamine	
	Per Patient	Per Patient per km	Per Patient	Per Patient per km
Naas	7.12 ± 1.52	$8.90 \times 10^{-2} \pm 1.90 \times 10^{-2}$	0.809 ± 0.181	$1.01 \times 10^{-2} \pm 2.27 \times 10^{-3}$
Mangweni	6.80 ± 1.53	$8.83 \times 10^{-2} \pm 1.99 \times 10^{-2}$	0.786 ± 0.170	$1.02 \times 10^{-2} \pm 2.21 \times 10^{-3}$
Mean	**6.96 ± 1.53**	$\mathbf{8.86 \times 10^{-2} \pm 1.95 \times 10^{-2}}$	**0.798 ± 0.176**	$\mathbf{1.02 \times 10^{-2} \pm 2.24 \times 10^{-3}}$

Table 4.35. Results of the Monte Carlo simulation for transport costs. ZAR 1.00 = US$ 0.217.

4.3. Fixed Costs

4.3.1. *In-service Training*

4.3.1.1. *Calculation of Costs*

During 1997, one training session for clinicians and nursing staff was held at Shongwe Hospital (in tandem with three others at Themba, Barberton and Rob Ferreira Hospitals). Another session was held for clinic nursing staff in the Tonga district (supplying training for staff at Mangweni and Naas Clinics, among others). Another clinic training session was held in the Shongwe district, but is not relevant to this study. Consumable costs were negligible. Staff attendance at the training session in Tonga was assumed to be 2 nurses per clinic, of which there are 11 in the district, for a total of 22 attendees (D Dürrheim, Communicable Diseases Consultant for the Mpumalanga Department of Health and Welfare). Consumable costs in the form of petrol were calculated for 93% octane at an estimated fuel consumption of 10 litres per 100 kilometres, at a mean 1997 fuel price of R 2.20 per litre (J Smalberger, Shell Cape Town). Consumable costs were assessed only for the Communicable Diseases Consultant, who made the trip from Nelspruit to Tonga and back. The total distance covered was 246 kilometres.

The post of Communicable Diseases Consultant carried a 1997 remuneration package of R304611.96 p.a. including benefits. The post of Communicable Disease Control Coordinator accounted for an annual salary of R 50 341.20 including benefits. (personal communication, R Raubenheimer, Personnel, Mpumalanga Department of Health and Welfare.) Other salary information is presented in Appendix A and sections 4.2.2 and 4.3.3.

Some *ad hoc* malaria training was also given to clinical staff by doctors based at Shongwe Hospital, but since this training occurred during the completion of the normal duties assigned to the trainers and trainees, and no consumables were used, costs were assumed to be negligible.

Equation 13 (p 38) was used in calculations.

Position	No of Staff (Q_{Ti})	Training Days (Day_{Ti})	Pro-portion. (R_{Ti})	Total Cost per Type (ZAR)	Con-sumable Cost (C_{Ti})	Cost per Trainee per Day (ZAR)	Total Training Cost (ITC_i) (ZAR)
Prof. nurse	2	1	1.00	121.87	0.00	121.87	243.74
Communicable Diseases Consultant	1	1	0.09*	833.98	54.12**	40.37	80.74
Communicable Disease Control Coordinators	2	1	0.09	137.83	0.00	12.53	25.06
Total							**349.54**

Table 4.36. Training costs for Naas and Mangweni Clinic staff in 1997. Both clinics contributed an equal number of staff (2) to the training sessions. ZAR 1.00 = US$ 0.217.

*** 2 staff from each of Naas and Mangweni Clinics, of 22 total attendees.**

**** Fuel costs, assessed as R 2.20/l, 246 km at a fuel consumption of 10 l per 100 km.**

Position	No of Staff (Q_{Ti})	Training Days (Day_{Ti})	Proportion. (R_{Ti})	Total Cost per Type (ZAR)	Consumable Cost (C_{Ti})	Cost per Trainee per Day (ZAR)	Total Training Cost (ITC_i) (ZAR)
Medical Officer	12	1	1.00	462.28	0.00	462.28	5 547.36
Nurse, Prof.	11	1	1.00	243.75	0.00	243.75	2 681.25
Nurse, Prof, Sen	1	1	1.00	303.62	0.00	303.62	303.62
Staff Nurse	6	1	1.00	166.44	0.00	166.44	998.64
Staff Nurse, Sen	2	1	1.00	196.90	0.00	196.90	393.80
Communicable Diseases Consultant	1	1	1.00	833.98	39.71	27.30	873.69
Specialist Physician	1	1	1.00	682.78	39.71	22.58	722.49
TOTAL							11 520.85

Table 4.37. Training costs for Shongwe Hospital staff in 1997. ZAR 1.00 = US$ 0.217.

*** It was estimated that 12 doctors (Medical Officers) and 20 nurses attended the Shongwe course (D Dürrheim). 20 nurses represent 13.61% of the hospital's total nursing complement; this percentage was used to estimate the numbers of each nursing pay class attending the course.**

**** Fuel costs, assessed as R 2.20/l, 190 km at a fuel consumption of 10 l per 100 km.**

4.3.1.2. *Shongwe Hospital Training Costs: Proportion Attributable to the Study Clinics in 1997*

The proportion of in-service training costs at Shongwe Hospital applicable to patients presenting at the study clinics in 1997 was calculated using the ratios derived in Section 4.2.3 ('Proportion of Total Shongwe Admissions').

Study Clinic	Total Cost of In-Service Malaria Training at Shongwe in 1997 (ZAR)	Proportion of Total Shongwe Malaria Cases (est 10354.13)	Total Cost of In-Service Training Attributable to Clinic Patients (ZAR)
Naas	11520.85	3.61%	415.90
Mangweni	11520.85	4.15%	478.12

Table 4.38. In-service training costs at Shongwe Hospital attributable to study clinic patients. Assuming *R*=0.3354 ± 0.07188, the total number of patients referred to Shongwe Hospital by all the clinics within its feeder district was 2 191.84 ± 468.74. A total of 6 535 malaria cases were ntoified in the Nkomazi region, encompassing Shongwe and Tonga. ZAR 1.00 = US$ 0.217.

The number of malaria referrals from each clinic is dependent on *R*, and the total number of hospital admissions for malaria received from all sources in the feeder region is also dependent on *R*. All sources with the hospital's feeder district are assumed to be using the same agent. By this reasoning, it follows that the proportion of study clinic referrals in relation to the hospital's total malaria admissions will remain constant, regardless of the first-line antimalarial agent. Therefore, costs for in-service training are constant and do not vary according to the choice of drug.

It is assumed that each drug or combination requires equal training.

4.3.1.3. Summary

Clinic	Total In-Service Training Cost of Malaria in 1997 (ZAR)		Difference in Cost per Patient (ZAR)
	Chloroquine	Sulfadoxine-Pyrimethamine	
Naas	3.24	3.24	0.00
Mangweni	3.05	3.05	0.00
Mean	**3.15**	**3.15**	**0.00**

Table 4.39. Summary of in-service training costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and sulfadoxine-pyrimethamine as first-line agents. The per-clinic staff costs (R349.54) have been added to referral costs in all of the above figures. ZAR 1.00 = US$ 0.217.

4.3.2. Maintenance

Total annual maintenance costs for each of the 24-hour clinics at Naas and Mangweni was estimated to be R4 000.00 by the Department of Health and Welfare (S Mabuza, Eerstehoek-Carolina District, Mpumalanga). Total expenditure at Shongwe Hospital in this category in 1997 was R88 378.67 (D Nkosi, Shongwe District). Costs were estimated by means of equation (13).

Naas Clinic

Drug	Resistance Adjustment (*R*)	Adjusted Number of Malaria Patients	Adjusted Maintenance Cost of Malaria in 1997 (ZAR)	Est. Total Naas Malaria Referrals in 1997	Proportion of Total Shongwe Admissions	Shongwe Maintenance Cost of Referred Malaria (ZAR)	Total 1997 Cost (ZAR)
CQ	1.34 ± 0.072	315.15 ± 16.96	28.11 ± 1.51	79.15 ± 16.96	0.563% ± 0.121%	497.55 ± 106.63	525.66 ± 108.14
SP	1.04 ± 0.008	245.09 ± 1.96	21.90 ± 0.18	9.09 ± 1.96	0.065% ± 0.014%	57.40 ± 12.57	79.30 ± 12.55

Table 4.40. Total maintenance costs due to malaria at Naas Clinic in 1997, based upon a chloroquine resistance prevalence of 47.92%, a sulfadoxine-pyrimethamine resistance prevalence of 5.50% and a patient return rate of 70% ± 15%. ZAR 1.00 = US$ 0.217.

Mangweni Clinic

Drug	Resistance Adjustment (*R*)	Adjusted Number of Malaria Patients	Adjusted Maintenance Cost of Malaria in 1997 (ZAR)	Est. Total Naas Malaria Referrals in 1997	Proportion of Total Shongwe Admissions	Shongwe Maintenance Cost of Referred Malaria (ZAR)	Total 1997 Cost (ZAR)
CQ	1.34 ± 0.072	361.89 ± 19.48	39.50 ± 2.13	90.89 ± 19.48	0.646% ± 0.138%	570.92 ± 122.35	610.41 ± 124.48
SP	1.04 ± 0.008	281.43 ± 2.25	30.78 ± 0.25	10.43 ± 2.25	0.075% ± 0.016%	65.91 ± 14.21	96.70 ± 14.46

Table 4.41. Total maintenance costs due to malaria at Mangweni Clinic in 1997, based upon an incidence of chloroquine resistance of 47.92%, a sulfadoxine-pyrimethamine resistance prevalence of 5.50% and a patient return rate of 70% ± 15%. ZAR 1.00 = US$ 0.217.

Clinic	Total Maintenance Cost (Per Patient) of Malaria in 1997 (ZAR)		Difference in Cost per Patient (ZAR)
	Chloroquine	Sulfadoxine-Pyrimethamine	
Naas	2.23 ± 0.46	0.34 ± 0.05	1.89 ± 0.41
Mangweni	2.25 ± 0.46	0.36 ± 0.05	1.90 ± 0.41
Mean Difference	**2.24 ± 0.46**	**0.35 ± 0.05**	**1.89 ± 0.41**

Table 4.42. Summary of maintenance costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine and sulfadoxine-pyrimethamine as first-line agents. ZAR 1.00 = US$ 0.217.

Simulation Results

Clinic	Total Maintenance Cost (Per Patient) of Malaria in 1997 ($\mu \pm \sigma$/ZAR)	
	Chloroquine	Sulfadoxine-Pyrimethamine
Naas	2.24 ± 0.45	0.335 ± 0.055
Mangweni	2.22 ± 0.48	0.337 ± 0.054
Mean	**2.23 ± 0.46**	**0.336 ± 0.054**

Table 4.43. Results of the Monte Carlo simulation for maintenance costs. ZAR 1.00 = US$ 0.217.

4.3.3. *Administrative & Support Staff*

4.3.3.1. *Administrative & Support Staff Makeup and Salaries*

Naas & Mangweni Clinics

Position Category	Number of staff per clinic (Q_i)	Monthly wage or salary (ZAR) (W_i)	Annual fringe benefits (ZAR) (FB_i)	Total annual cost of position including benefits (ZAR) $((Q_i \times [(T_i \times W_i) + FB_i]))$
Admin. clerk	1	2 138.55	10 263.60	35 922.60
Cleaner	5	1 583.50	7 600.80	13 3014.00
Groundsman	1	1 583.50	7 600.80	26 602.80
Total	7			**195 539.40**

Table 4.44. Total salaries and benefits paid to support and administrative staff at each of the clinics at Naas and Mangweni in 1997, as well as numbers of staff per job description. ZAR 1.00 = US$ 0.217.

Shongwe Hospital

Position Category	Number of staff (Q_i)	Monthly wage or salary (ZAR) (W_i)	Annual fringe benefits (ZAR) (FB_i)	Total annual cost of position including benefits (ZAR) $((Q_i \times [(T_i \times W_i) + FB_i]))$
Admin	46	See Appendix A	See Appendix A	1 859 827.20
General & Domestic	230			6 271 801.20
Maintenance	21			558 658.80
Lab Services	8			498 556.80
Total	305			**9 188 844.00**

Table 4.45. Total salaries and benefits paid to administrative and support staff cadres at Shongwe Hospital in 1997, as well as numbers of staff per category. Subcategories and details of wages and benefits appear in Appendix A. ZAR 1.00 = US$ 0.217.

4.3.3.2. *Proportion of Costs due to Malaria*

Naas Clinic

Drug	CQ Resistance Adjustment (*R*)	Adjusted Number of Malaria Patients	Adjusted Clinic Staff Cost of Malaria in 1997 (ZAR)	Est. Total Naas Malaria Referrals in 1997	Proportion of Total Shongwe Admissions	Shongwe Staff Cost of Referred Malaria (ZAR)	Total 1997 Cost (ZAR)
CQ	1.3354 ± 0.07188	315.15 ± 16.96	1 374.39 ± 73.98	79.15 ± 16.96	0.563% ± 0.121%	51 730.72 ± 11 086.48	53 105.11 ± 11 160.45
SP	1.0385 ± 0.0083	245.09 ± 1.96	1 070.50 ± 8.56	9.09 ± 1.96	0.065% ± 0.014%	5 967.82 ± 1 286.57	7 038.32 ± 1 295.13

Table 4.46. Total support and administrative staff costs due to malaria at Naas Clinic in 1997, based upon a chloroquine resistance prevalence of 47.92%, a sulfadoxine-pyrimethamine resistance prevalence of 5.50%, and a patient return rate of 70% ± 15%. ZAR 1.00 = US$ 0.217.

Mangweni Clinic

Drug	CQ Resistance Adjustment (*R*)	Adjusted Number of Malaria Patients	Adjusted Clinic Staff Cost of Malaria in 1997 (ZAR)	Est. Total Naas Malaria Referrals in 1997	Proportion of Total Shongwe Admissions	Shongwe Staff Cost of Referred Malaria (ZAR)	Total 1997 Cost (ZAR)
CQ	1.3354 ± 0.07188	361.89 ± 19.48	1 930.90 ± 103.93	90.89 ± 19.48	0.646% ± 0.138%	59 358.78 ± 12 721.25	61 289.67 ± 12 825.19
SP	1.0385 ± 0.0083	281.43 ± 2.25	1 504.90 ± 12.03	10.43 ± 2.25	0.075% ± 0.016%	6 852.88 ± 1 477.37	8 357.79 ± 1 489.40

Table 4.47. Total support and administrative staff costs due to malaria at Mangweni Clinic in 1997, based upon a chloroquine resistance prevalence of 47.92%, a sulfadoxine-pyrimethamine resistance prevalence of 5.50%, and a patient return rate of 70% ± 15%. ZAR 1.00 = US$ 0.217.

Shongwe Hospital

Staff costs related to malaria referrals from the two study clinics were relevant, and were thus calculated.

47.92% of the malaria cases detected at Naas and Mangweni, based upon the results of the *in vivo* study of chloroquine resistance in the region (summarized in Section 4.2), are assumed to have been resistant to chloroquine. Assuming that all recrudescent patients returned to the same clinic where they were treated, and were referred to Shongwe Hospital as per protocol, staff costs are adjusted accordingly by applying the *R* modifier (see Section 4.2.1).

During the period January to December 1997, Shongwe Hospital recorded an estimated 13990 admissions and 53 083 outpatient visits.* For the purposes of this study, only admissions arising from clinic referrals are considered.

4.3.3.3. *Summary*

Clinic	Total Staff Cost (Per Patient) of Malaria in 1997 (ZAR)		Difference in Cost per Patient (ZAR)
	Chloroquine	**Sulfadoxine-Pyrimethamine**	
Naas	225.02 ± 47.29	29.82 ± 5.49	195.20 ± 41.80
Mangweni	226.16 ± 47.33	30.84 ± 5.50	195.32 ± 41.83
Mean Difference	**225.59 ± 47.31**	**30.33 ± 5.49**	**195.26 ± 41.82**

Table 4.48. Summary of support & administrative staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and sulfadoxine-pyrimethamine as first-line agents. ZAR 1.00 = US$ 0.217.

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* Owing to the permanent non-availability of the inpatient and outpatient totals for August 1997, the mean of the other 11 months was substituted as the total for that month in all calculations, including the determination of the year's total. Seasonal fluctuations were assumed to be insignificant.

Clinic	Total Administrative & Support Staff Cost (Per Patient) of Malaria in 1997 (μ ± σ/ZAR)	
	Chloroquine	Sulfadoxine-Pyrimethamine
Naas	226.04 ± 47.09	29.69 ± 5.68
Mangweni	224.09 ± 49.19	29.92 ± 5.52
Mean	**225.07 ± 48.14**	**29.81 ± 5.60**

Table 4.49. Results of the Monte Carlo simulation for administrative and support staff costs. ZAR 1.00 = US$ 0.217.

4.3.4. *Utilities*

Naas & Mangweni

Utility	Mean Cost per month per clinic (ZAR)	Cost per clinic per annum (ZAR)
Electricity	1 200.00	14 400.00
Postage	12.82	153.85
Telephone	2 000.00	24 000.00
Water	Free	Free
Total	**3 212.82**	**38 553.84**

Table 4.50. Mean utilities costs for each of the 24-hour clinics at Naas and Mangweni in the Tonga district (A Khoza, Administrative Officer, Tonga District). The costs are those for the 1997-1998 financial year; since they are mean costs, they are assumed to be relevant for the 1997 calendar year also. ZAR 1.00 = US$ 0.217.

Shongwe Hospital

Utility	1997 Expenditure
Electricity	418 954.06
Postage	2 000.00
Telephone	235 813.25
Water	Free
Total	656 767.31

Table 4.51. Utilities costs for Shongwe Hospital in 1997 (figures courtesy of Shongwe District administration). ZAR 1.00 = US$ 0.217.

4.3.4.1. *Proportion of Utility Costs due to Malaria*

Naas Clinic

Drug	CQ Resistance Adjustment (*R*)	Adjusted Number of Malaria Patients	Adjusted Clinic Staff Cost of Malaria in 1997 (ZAR)	Est. Total Naas Malaria Referrals in 1997	Proportion of Total Shongwe Admissions	Shongwe Staff Cost of Referred Malaria (ZAR)	Total 1997 Cost (ZAR)
CQ	1.34 ± 0.072	315.15 ± 16.96	270.98 ± 14.59	79.15 ± 16.96	0.563% ± 0.121%	3 697.42 ± 792.40	3 968.41 ± 806.99
SP	1.04 ± 0.008	245.09 ± 1.96	211.07 ± 1.69	9.09 ± 1.96	0.065% ± 0.014%	426.55 ± 91.96	637.61 ± 93.64

Table 4.52. Total utility costs due to malaria at Naas Clinic in 1997, based upon a chloroquine resistance prevalence of 47.92%, a sulfadoxine-pyrimethamine resistance prevalence of 5.50%, and a patient return rate of 70% ± 15%. ZAR 1.00 = US$ 0.217.

Mangweni Clinic

Drug	CQ Resistance Adjustment (R)	Adjusted Number of Malaria Patients	Adjusted Clinic Staff Cost of Malaria in 1997 (ZAR)	Est. Total Naas Malaria Referrals in 1997	Proportion of Total Shongwe Admissions	Shongwe Staff Cost of Referred Malaria (ZAR)	Total 1997 Cost (ZAR)
CQ	1.34 ± 0.072	361.89 ± 19.48	380.71 ± 20.49	90.89 ± 19.48	0.646% ± 0.138%	4 242.63 ± 909.24	4 623.34 ± 929.74
SP	1.04 ± 0.008	281.43 ± 2.25	296.72 ± 2.37	10.43 ± 2.25	0.075% ± 0.016%	489.81 ± 105.59	786.52 ± 107.97

Table 4.53. Total utility costs due to malaria at Mangweni Clinic in 1997, based upon a chloroquine resistance prevalence of 47.92%, a sulfadoxine-pyrimethamine resistance prevalence of 5.50%, and a patient return rate of 70% ± 15%. ZAR 1.00 = US$ 0.217.

4.3.4.2. *Summary*

Clinic	**Total Utility Cost (Per Patient) of Malaria in 1997 (ZAR)**		**Difference in Cost per Patient (ZAR)**
	Chloroquine	**Sulfadoxine-Pyrimethamine**	
Naas	16.82 ± 3.42	2.70 ± 0.40	14.11± 3.02
Mangweni	17.06 ± 3.43	2.90 ± 0.40	14.16 ± 3.03
Mean Difference	**16.94 ± 3.43**	**2.80 ± 0.40**	**14.14 ± 3.03**

Table 4.54. Summary of utility costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine and sulfadoxine-pyrimethamine as first-line agents. ZAR 1.00 = US$ 0.217.

Clinic	Total Utility Cost (Per Patient) of Malaria in 1997 (μ ± σ/ZAR)	
	Chloroquine	**Sulfadoxine-Pyrimethamine**
Naas	16.89 ± 3.41	2.69 ± 0.41
Mangweni	16.75 ± 3.56	2.71 ± 0.40
Mean	**16.82 ± 3.49**	**2.70 ± 0.40**

Table 4.55. Results of the Monte Carlo simulation for utility costs. ZAR 1.00 = US$ 0.217.

4.4. Summary

4.4.1. *Variable Costs*

Cost Category	Costs Arising from Malaria Cases Presenting at the Study Clinics of Naas and Mangweni during 1997		
	CQ	**SP**	**Difference**
Drug Costs	29.29 ± 14.80	18.04 ± 1.71	11.55 ± 13.10
Clinical Staff Costs	110.83 ± 43.79	16.89 ± 5.06	93.94 ± 38.74
Consumables	36.38 ± 8.47	20.52 ± 0.98	15.859 ± 7.498
Transport	6.95 ± 1.49	0.80 ± 0.18	6.153 ± 1.318
Total	**183.45 ± 68.55**	**56.25 ± 7.93**	**127.20 ± 60.62**

Table 4.56. Summary of differences in modelled variable costs per patient during 1997, when comparing chloroquine to sulfadoxine-pyrimethamine. ZAR 1.00 = US$ 0.217.

Cost Category	Costs Arising from Malaria Cases Presenting at the Study Clinics of Naas and Mangweni during 1997	
	CQ	SP
Drug Costs	30.54 ± 10.61	18.14 ± 1.21
Clinical Staff Costs	111.27 ± 26.82	16.91 ± 3.10
Consumables	66.90 ± 11.40	24.01 ± 1.32
Transport	6.96 ± 1.53	0.798 ± 0.176
Total	**215.67 ± 50.36**	**59.86 ± 5.81**

Table 4.57. Summary of differences in modelled variable costs per patient during 1997, when comparing chloroquine to sulfadoxine-pyrimethamine. These data were a product of the Monte Carlo simulation process. ZAR 1.00 = US$ 0.217.

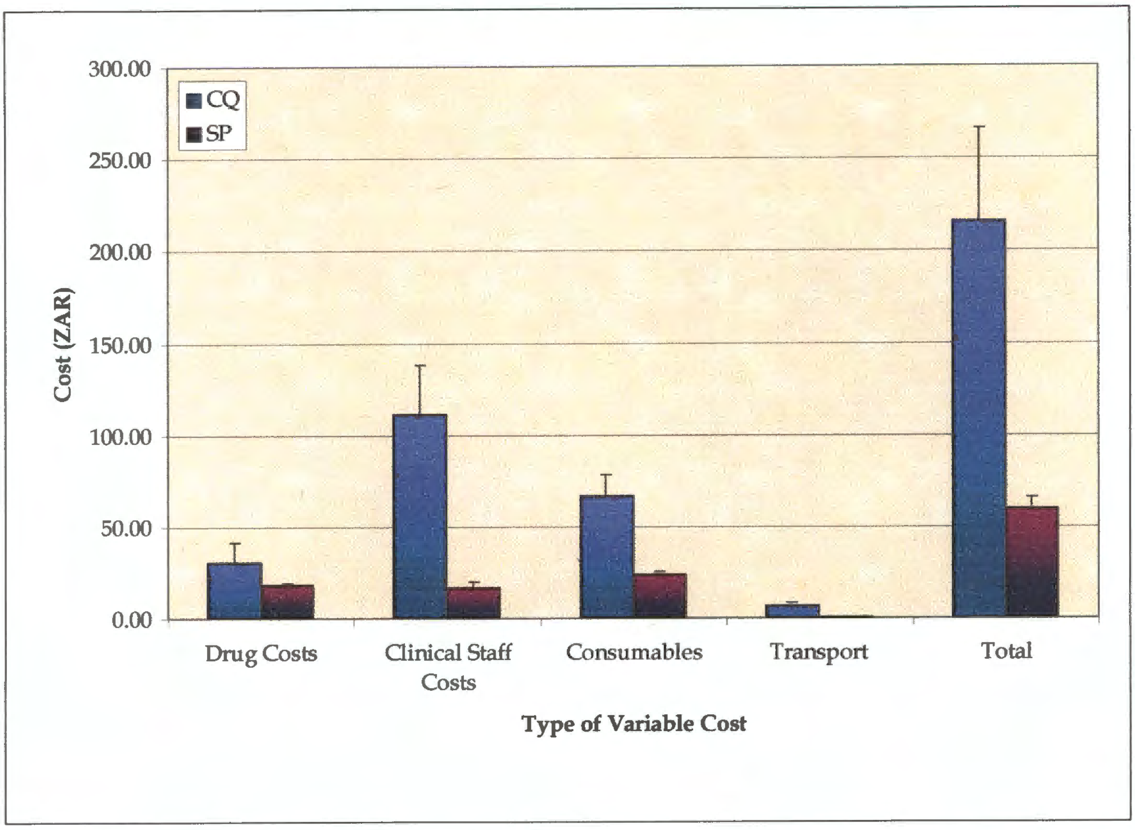

Figure 4.7. Comparison of variable costs per notified patient involved when comparing chloroquine to sulfadoxine-pyrimethamine as first-line therapy for mild malaria. Use of sulfadoxine-pyrimethamine results in a 72.24% ± 20.66% reduction in costs, a total of R155.81 ± R44.55 per notified patient. ZAR 1.00 = US$ 0.217.

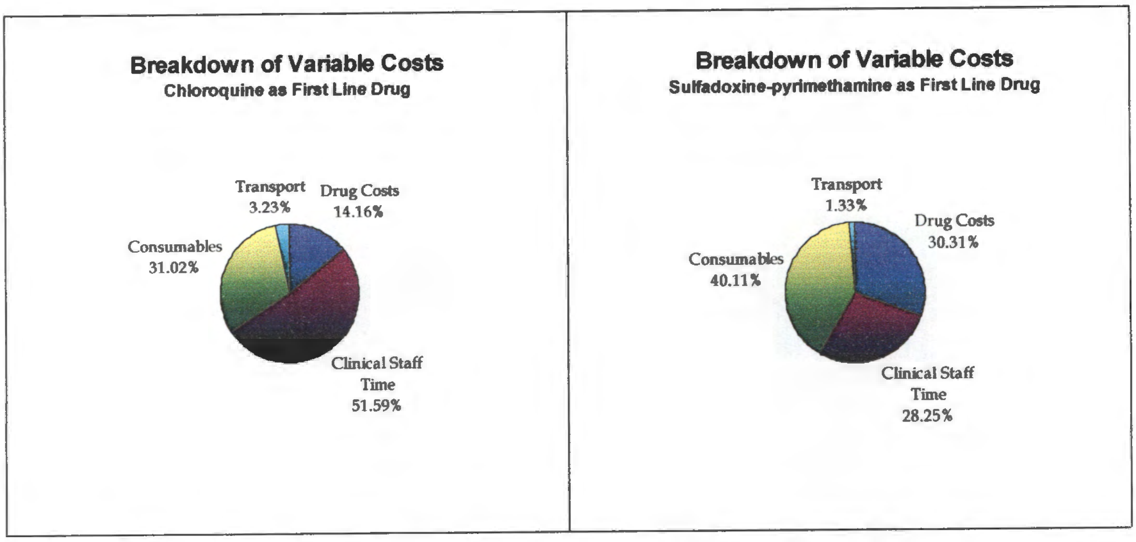

Figure 4.8. Comparison of variable costs between CQ and SP regimen models.

4.4.2. *Fixed Costs*

Cost Category	Costs Arising from Malaria Cases Presenting at the Study Clinics of Naas and Mangweni during 1997		
	CQ	SP	Difference
In-service Training	3.15	3.15	0.00
Maintenance	2.24 ± 0.46	0.35 ± 0.05	1.89 ± 0.41
Administrative & Support Staff Time	225.59 ± 47.31	30.33 ± 5.49	195.26 ± 41.82
Utility Costs	16.94 ± 3.43	2.80 ± 0.40	14.14 ± 3.03
Total	**247.92 ± 51.20**	**36.63 ± 5.94**	**211.29 ± 45.26**

Table 4.58. Summary of differences in mean fixed costs per patient during 1997, when comparing chloroquine to sulfadoxine-pyrimethamine. ZAR 1.00 = US$ 0.217.

Cost Category	Costs Arising from Malaria Cases Presenting at the Study Clinics of Naas and Mangweni during 1997	
	CQ	SP
In-service Training	3.15	3.15
Maintenance	2.23 ± 0.46	0.336 ± 0.054
Administrative & Support Staff Time	225.07 ± 48.14	29.81 ± 5.60
Utility Costs	16.82 ± 3.49	2.70 ± 0.40
Total	**247.27 ± 52.09**	**36.00 ± 6.05**

Table 4.59. Summary of differences in modelled fixed costs per patient during 1997, when comparing chloroquine to sulfadoxine-pyrimethamine. These data were a product of the Monte Carlo simulation process. ZAR 1.00 = US$ 0.217.

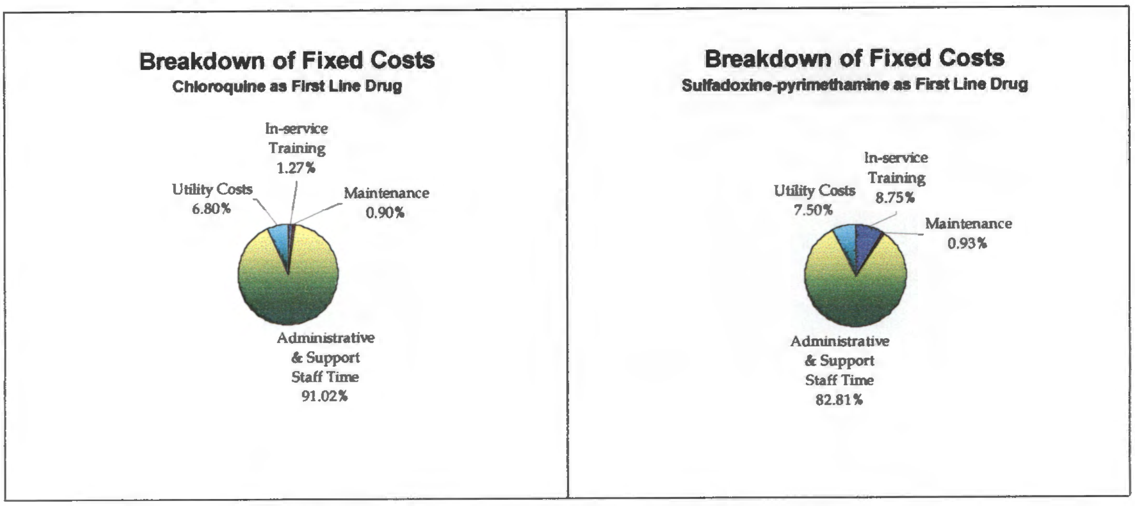

Figure 4.9. Comparison of fixed costs between CQ and SP regimen models.

4.4.3. *Combined Variable and Fixed Costs*

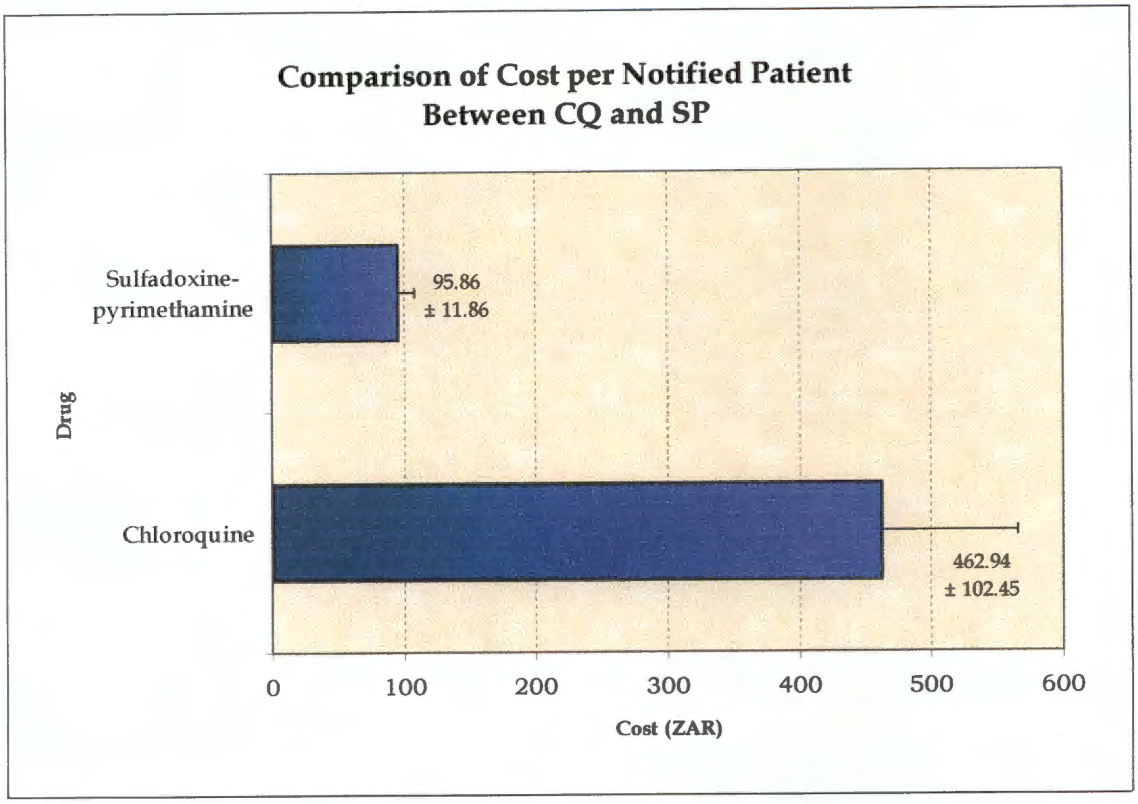

Figure 4.10. Combination of variable and fixed costs produces a final result: the use of chloroquine as first line agent against malaria in the Tonga district in 1997 was estimated to cost the health care system R462.94 ± R102.45 per notified patient. Sulfadoxine-pyrimethamine, in comparison, cost R95.86 ± R11.86 per notified patient, representing a saving of 79.29% ± 19.57% per notified patient. ZAR 1.00 = US$ 0.217.

4.4.4. *Differences in Benefits Determined by Choice of First-line Drug*

Clinic	Benefits			
	Chloroquine		Sulfadoxine-pyrimethamine	
	Clinic Visits	Hospital Patient Days	Clinic Visits	Hospital Patient Days
Naas	79.15 ± 16.96	237.46 ± 50.89	9.09 ± 1.96	27.26 ± 5.88
Mangweni	90.89 ± 19.48	272.68 ± 58.44	10.43 ± 2.25	31.30 ± 6.75

Table 4.60. Differences in benefits, as influenced by choice of first-line drug. Using SP as first-line therapy at the study clinics would result in an 88.5% ± 21.5% mean drop in clinic visits and patient days at hospital level.

4.4.5. *Cost-effectiveness*

Using chloroquine as the baseline drug, the average cost-effectiveness ratio results are as follows:

Drug	ACER
Chloroquine	1.000
Sulfadoxine-pyrimethamine	4.829

Table 4.61. ACERs of the study drugs, compared in terms of modelled fixed and variable costs.

Drug	Average Benefits Ratio
Chloroquine	1.000
Sulfadoxine-pyrimethamine	8.707

Table 4.62. Average benefits ratios of the study drugs, comparing benefits in terms of clinic visits and hospital patient days saved.

MODELLING OF ALTERNATIVE DRUGS

Apart from sulfadoxine-pyrimethamine and chloroquine, several other antimalarial drugs are potentially suitable as first-line therapy for mild malaria. These include halofantrine, pyronaridine, mefloquine, artesunate, co-artemether and the atovaquone-proguanil combination.

As before, the number of decimal places used in the presentation of R-values for the various drug models has been limited to two for the sake of clarity, although the full number was used in all calculations.

5.1. Amodiaquine

Recently, a case has been made for amodiaquine to be brought back into use as an antimalarial agent (White, 1996; Olliaro, 1996).

A systematic review of amodiaquine treatment in uncomplicated malaria published by Olliaro *et al* in 1996 indicated that, by day 14 of treatment, 85.44% (657 of 769) of patients treated with amodiaquine showed parasitological success. The review covered a total of 15 studies, 9 of which compared amodiaquine with chloroquine, and the remaining 6 of which compared amodiaquine with sulfadoxine-pyrimethamine. The overwhelming majority of studies were conducted in Africa.

However, in results from the 4 studies that evaluated patients to day 28, all of which compared amodiaquine to sulfadoxine-pyrimethamine, the mean parasitological success rate fell to 63.21%.

5.1.1. *Derivation of* R

Using the review published by Olliaro *et al*, and applying the principles developed in Section 5.2.1, R_{AM} was derived as follows:

$$R_{AM} = 0.3679 \times (0.7 \pm 0.15)$$
$$R_{AM} = 0.2575 \pm 0.05519$$

It was decided to use the 28-day parasitological failure rate of 36.79% as an estimate of resistance, bearing in mind the 76% resistance prevalence found in Mozambique (Schapira & Schwalbach, 1988). Freese *et al* found an *in vitro* resistance prevalence of 40% (2 of 5 isolates) to amodiaquine in *P. falciparum* isolates collected in the then-Transvaal, now Northern Province and Mpumalanga (Freese *et al*, 1993). This lends credibility to the results found by the Olliaro review.

5.1.2. *Variable Costs*

5.1.2.1. *Drug Costs*

Amodiaquine is not currently registered in South Africa. The export price for the Parke-Davis product is ca US$ 22.00, for a box of 500 200mg tablets (personal communication, P Olliaro). This, using a mean 1997 ZAR/US$ exchange rate of 4.6072 (Olsen & Associates, http://www.oanda.com), gives us an estimated South African price of R101.36 per 500 tablets.

Dosage is 10 mg/kg once daily for 3 days.

Estimation of Drug Cost per Patient: Amodiaquine

Drug dosages, and hence costs, for patients of different ages and gender were estimated by means of the National Center for Health Statistics data used in the estimation of quinine dosage (see Section 5.2.2.3). These data allowed weights to be inferred from ages. Weight allowed dose, and hence cost, to be estimated.

Clinic	No. of Malaria Notifications in 1997	Total AM Cost (ZAR)	Mean AM cost per Patient (ZAR)
Naas	236	408.02	1.73
Mangweni	271	455.28	1.68
Mean			**1.70 (US$ 0.37)**

Table 5.1. Modelled cost of amodiaquine first-line therapy at the study clinics in 1997. US$1.00 = ZAR 4.6072.

Estimation of Drug Cost per Patient: Quinine

Clinic	No. of patients in 1997	*R*	Est. no. of referrals	Cost to treat with IV Quinine (ZAR)		Cost to treat with PO Quinine (ZAR)	
				Per patient	Adj. (Referrals x 0.7 ± 0.15)	Per patient	Adj. (Referrals x 0.3 ± 0.15)
Naas	236	0.26 ± 0.06	60.77 ± 13.02	112.10	4768.62 ± 2262.92	30.50	556.05 ± 456.79
						Total for Naas (IV + PO)	**5324.67 ± 2719.71**
Mangweni	271	0.26 ± 0.06	69.78 ± 14.96	108.95	5321.96 ± 2525.50	29.66	620.92 ± 510.09
						Total for Mangweni (IV + PO)	**5942.97 ± 3035.59**

Table 5.2. Calculation of quinine costs per clinic, assuming first-line drug is amodiaquine (R=0.26 ± 0.06). US$1.00 = ZAR 4.6072.

Summary

Study Clinic	**Amodiaquine Cost (ZAR)**		
	AM Cost	**Quinine Cost**	**Total Cost**
Naas	408.02	5 324.67 ± 2 719.71	5 732.69 ± 2 719.71
Mangweni	455.28	5 942.97 ± 3 035.59	6 398.17 ± 3 035.59

Table 5.3. Total projected 1997 drug costs for the treatment of patients originating at the study clinics; amodiaquine is used as study drug. US$1.00 = ZAR 4.6072.

Clinic	Total Drugs Cost (Per Patient) of Malaria in 1997 (Amodiaquine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	24.29 ± 11.52	25.61 ± 8.47
Mangweni	23.61 ± 11.20	24.86 ± 8.29
Mean	**23.95 ± 11.36**	**25.24 ± 8.38**

Table 5.4. Summary of drug costs of malaria cases originating at Naas (236 cases) and Mangweni (271 cases) Clinics in 1997, using chloroquine and amodiaquine as first-line agents. US$1.00 = ZAR 4.6072.

5.1.2.2. *Clinical Staff Costs*

Clinical staff costs were assessed according to the model developed in section 4.2.2.2.

Clinic	Total Clinical Staff Cost (Per Patient) of Malaria in 1997 (Amodiaquine) (ZAR)	
	Point Estimate	Simulation
Naas	86.19 ± 33.63	86.62 ± 20.11
Mangweni	86.19 ± 33.63	86.13 ± 21.02
Mean	86.19 ± 33.63	86.38 ± 20.57

Table 5.5. Summary of clinical staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using amodiaquine as first-line agent. US$1.00 = ZAR 4.6072.

5.1.2.3. *Consumables*

R is the only factor to change in the estimation of $Cost_C$ in amodiaquine. Otherwise, costs are calculated as in section 4.2.3.

Clinic	Total Consumables Cost of Malaria in 1997 (Amodiaquine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	44.51 ± 14.25	51.72 ± 8.62
Mangweni	52.57 ± 14.25	59.61 ± 8.98
Mean	**48.54 ± 14.25**	**55.67 ± 8.80**

Table 5.6. Summary of consumable costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and amodiaquine as first-line agents. US$1.00 = ZAR 4.6072.

5.1.2.4. *Transport*

Since the equation for transport costs is a product, $Cost_T$ may be estimated for amodiaquine simply by substituting *R*. Where $Cost_{TCQ}$ is the transport cost for chloroquine and $Cost_{TAM}$ is the transport cost for amodiaquine, we have

$$Cost_{TAM} = \frac{Cost_{TCQ}}{R_{CQ}} \times R_{AP} \qquad 19$$

$Cost_{TCQ}$ is R1671.74 ± R358.27 at Naas Clinic, R_{CQ}=0.3354 ± 0.07188, and R_{AM}=0.2575 ± 0.05519. Therefore, $Cost_{TAM}$ for Naas is R1 283.46 ± R275.08 (US$ 278.51 ± US$ 59.69).

Similarly, $Cost_{TAM}$ for Mangweni Clinic was estimated to be R1 418.54 ± R304.04 (US$ 307.82 ± US$ 65.98).

Clinic	Total Per-Patient Transport Costs of Malaria in 1997, using Amodiaquine (ZAR/km)			
	Point Estimate		Monte Carlo Simulation	
	Per Patient	Per Patient per km	Per Patient	Per Patient per km
Naas	5.44 ± 1.17	6.80×10^{-2} $\pm 1.46 \times 10^{-2}$	5.48 ± 1.20	6.84×10^{-2} $\pm 1.50 \times 10^{-2}$
Mangweni	5.23 ± 1.29	7.81×10^{-2} $\pm 1.67 \times 10^{-2}$	5.26 ± 1.19	6.83×10^{-2} $\pm 1.55 \times 10^{-2}$
Mean	**5.34 ± 1.23**	7.30×10^{-2} $\pm 1.57 \times 10^{-2}$	**5.37 ± 1.20**	6.84×10^{-2} $\pm 1.53 \times 10^{-2}$

Table 5.7. Summary of transport costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and amodiaquine as first-line agents. US$1.00 = ZAR 4.6072.

5.1.3. *Fixed Costs*

In-service training and capital are not affected by the choice of first-line drug, and are therefore not reflected as separate sections. In-service training, however, appears in the summaries for completeness. The point estimates for each category were calculated similarly to those in Section 4.3.

5.1.3.1. *Administrative & Support Staff*

Clinic	Per-Patient Staff Time Cost of Malaria in 1997 (Amodiaquine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	173.99 ± 36.36	175.11 ± 37.36
Mangweni	175.13 ± 36.39	174.68 ± 38.40
Mean	**174.56 ± 36.37**	**174.90 ± 37.88**

Table 5.8. Summary of administrative & support staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using amodiaquine as first-line agent. US$1.00 = ZAR 4.6072.

5.1.3.2. *Maintenance*

Clinic	Total Maintenance Cost (Per Patient) of Malaria in 1997 (Amodiaquine) (ZAR)	
	Point Estimate	**Monte Carlo Simulation**
Naas	1.73 ± 0.35	1.74 ± 0.362
Mangweni	1.76 ± 0.35	1.74 ± 0.372
Mean Difference	**1.75 ± 0.35**	**1.74 ± 0.367**

Table 5.9. Summary of maintenance costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine and amodiaquine as first-line agents. US$1.00 = ZAR 4.6072.

5.1.3.3. *Utilities*

Clinic	Per-Patient Utility Cost of Malaria in 1997 (Amodiaquine) (ZAR)	
	Point Estimate	**Monte Carlo Simulation**
Naas	13.13 ± 2.63	13.21 ± 2.70
Mangweni	13.36 ± 2.64	13.18 ± 2.78
Mean	**13.24 ± 2.63**	**13.20 ± 2.74**

Table 5.10. Summary of utility costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and amodiaquine as first-line agents. US$1.00 = ZAR 4.6072.

5.1.4. *Total Costs for Amodiaquine*

5.1.4.1. *Variable Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	**Monte Carlo Simulation**	**Point Estimate**	**Monte Carlo Simulation**
Drug Costs	24.29 ± 11.52	25.61 ± 8.47	23.61 ± 11.20	24.86 ± 8.29
Clinical Staff Costs	86.19 ± 33.63	86.62 ± 20.11	86.19 ± 33.63	86.13 ± 21.02
Consumables Costs	44.51 ± 14.25	51.72 ± 8.62	52.57 ± 14.25	59.61 ± 8.98
Transport Costs	5.44 ± 1.17	5.48 ± 1.20	5.23 ± 1.29	5.26 ± 1.19
Total	**160.43 ± 60.57**	**169.43 ± 38.40**	**167.60 ± 60.37**	**175.86 ± 39.48**

Table 5.11. Summary of variable costs at Naas and Mangweni Clinics in the event of amodiaquine being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.1.4.2. *Fixed Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	**Monte Carlo Simulation**	**Point Estimate**	**Monte Carlo Simulation**
In-service Training	3.24	3.24*	3.05	3.05*
Maintenance	1.73 ± 0.35	1.74 ± 0.362	1.76 ± 0.35	1.74 ± 0.372
Administrative & Support Staff Costs	173.99 ± 36.36	175.11 ± 37.36	175.13 ± 36.39	174.68 ± 38.40
Utility Costs	13.13 ± 2.63	13.21 ± 2.70	13.36 ± 2.64	13.18 ± 2.78
Total	**192.09 ± 39.34**	**193.30 ± 40.42**	**193.30 ± 39.38**	**192.65 ± 41.55**

Table 5.12. Summary of fixed costs at Naas and Mangweni Clinics in the event of amodiaquine being adopted as first-line therapy. US$1.00 = ZAR 4.6072. *Not modelled.

5.1.4.3. *Cost-effectiveness*

Clinic	Total Combined Fixed and Variable Cost per Patient	ACER
Naas	362.73 ± 78.82 *(US$ 78.71 ± US$ 17.10)*	1.267
Mangweni	368.51 ± 81.03 *(US$ 79.97 ± US$ 17.58)*	1.266
Mean	**365.62 ± 79.93** ***(US$ 79.34 ± US$ 17.34)***	**1.266**

Table 5.13. The cost-effectiveness of amodiaquine at the study clinics in 1997, compared with chloroquine. A mean total cost per notified patient of R462.94 ± R102.45 (US$ 100.46 ± US$ 22.23) was used for the chloroquine, the baseline. (ACER: average cost-effectiveness ratio.) US$1.00 = ZAR 4.6072.

5.2. Artemether-benflumetol (Co-artemether)

Two trials in children in Sub-Saharan Africa showed resistance to CGP 56697 in *P. falciparum*. A 15-day cure rate of 93.3% was recorded in The Gambia (van Seidlein *et al*, 1998), and in Kilombero, Tanzania, a 14-day cure rate of 86.4% was recorded (Hatz *et al*, 1998).

5.2.1. *Derivation of* R

Co-artemether has been in use for only a very short time, and has been tested by clinical trial in Sub-Saharan Africa and Southeast Asia, with mixed results. For the derivation of *R*, it was decided to use the cure rate of 93.3% reported by van Seidlein *et al* in the Gambia in 1998. The only other useful study, published in Tanzania, reports a higher level of resistance, but South Africa has not used artemisinin derivatives for the treatment of malaria, and so resistance *in vivo* is thought to be lower.

$$R_{AB} = 0.067 \times (0.7 \pm 0.15)$$
$$R_{AB} = 0.0469 \pm 0.01005$$

5.2.2. *Variable Costs*

5.2.2.1. *Drug Costs*

For the purposes of this study, the 6-dose schedule used by Looareesuwan *et al* in 1998 was modelled: an adult course was composed of a total of 480mg artemether combined with 2880mg benflumetol, or 6.86 mg/kg artemether plus 41.14 mg/kg benflumetol (assuming a mean adult weight of 70 kg).

The cost of a package of 16 tablets of Riamet from Novartis is 58.80 Swiss francs, which translates to R186.91 (at a mean 1997 exchange rate of 0.3146 Rands to the Swiss franc). A pack of 24 tablets costs 78.75 CHF, or R250.33 in mean 1997 Rands. (Exchange rates obtained from the website of Olsen & Associates, http://www.oanda.com.) Therefore, an adult course of 24 tablets (each containing 20mg artemether and 120mg benflumetol) would cost R250.33 (US$ 54.32).

Estimation of Drug Cost per Patient: Artemether-benflumetol

Clinic	No. of Malaria Notifications in 1997	Total AB Cost (ZAR)	Mean AP cost per Patient (ZAR)
Naas	236	44 162.52	187.13
Mangweni	271	49 276.76	208.80
Mean			**197.96 (US$ 42.96)**

Table 5.14. Modelled cost of artemether-benflumetol first-line therapy at the study clinics in 1997. US$1.00 = ZAR 4.6072.

Estimation of Drug Cost per Patient: Quinine

Clinic	No. of patients in 1997	R	Est. no. of referrals	Cost to treat with IV Quinine (ZAR)		Cost to treat with PO Quinine (ZAR)	
				Per patient	Adj. (Referrals x 0.7 ± 0.15)	Per patient	Adj. (Referrals x 0.3 ± 0.15)
Naas	236	0.05 ± 0.01	11.07 ± 2.37	112.10	868.54 ± 412.11	30.50	101.28 ± 83.19
Total for Naas (IV + PO)							**969.81 ± 495.30**
Mangweni	271	0.05 ± 0.01	12.71 ± 2.72	108.95	969.32 ± 459.93	29.66	113.09 ± 92.90
Total for Mangweni (IV + PO)							**1 082.41 ± 552.83**

Table 5.15. Calculation of quinine costs per clinic, assuming first-line drug is artemther-benflumetol (R=0.0469 ± 0.01005). US$1.00 = ZAR 4.6072.

Summary

Study Clinic	Co-artemether Cost (ZAR)		
	AB Cost	Quinine Cost	Total Cost
Naas	44 162.52	969.81 ± 495.30	45 132.33 ± 495.30
Mangweni	49 276.76	1 082.41 ± 552.83	50 359.17 ± 552.83

Table 5.16. Total projected 1997 drug costs for the treatment of patients originating at the study clinics; a comparison of chloroquine and co-artemether. US$1.00 = ZAR 4.6072.

Clinic	Total Drugs Cost (Per Patient) of Malaria in 1997 (Co-artemether) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	191.24 ± 2.10	191.38 ± 1.49
Mangweni	185.83 ± 2.04	185.95 ± 1.41
Mean	**188.53 ± 2.07**	**188.67 ± 1.45**

Table 5.17. Summary of drug costs of malaria cases originating at Naas (236 cases) and Mangweni (271 cases) Clinics in 1997, comparing chloroquine and co-artemether as first-line agents. US$1.00 = ZAR 4.6072.

5.2.2.2. *Clinical Staff Costs*

Clinic	Total Clinical Staff Cost (Per Patient) of Malaria in 1997 (Co-artemether) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	19.55 ± 6.12	19.57 ± 3.68
Mangweni	19.55 ± 6.12	19.48 ± 3.59
Mean	**19.55 ± 6.12**	**19.53 ± 3.64**

Table 5.18. Summary of clinical staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine and co-artemether as first-line agents. US$1.00 = ZAR 4.6072.

5.2.2.3. *Consumables*

Clinic	Total Consumables Cost per Patient of Malaria in 1997 (Co-artemether) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	19.91 ± 2.60	21.19 ± 1.56
Mangweni	27.97 ± 2.60	29.22 ± 1.53
Mean Difference	**23.94 ± 2.60**	**25.21 ± 1.55**

Table 5.19. Summary of consumable costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using co-artemether as first-line agent. US$1.00 = ZAR 4.6072.

5.2.2.4. *Transport*

$Cost_{TCQ}$ is R1 671.74 ± R358.27 at Naas Clinic, R_{CQ}=0.34 ± 0.072, and R_{AB}=0.05 ± 0.01. Therefore, $Cost_{THF}$ for Naas is R233.76 ± R50.09 (US$ 50.73 ± US$ 10.87).

Similarly, $Cost_{THF}$ for Mangweni Clinic was estimated to be R258.37 ± R55.36 (US$ 56.07 ± US$ 12.01).

Clinic	Total Per-Patient Transport Costs of Malaria in 1997 (Co-artemether) (ZAR/km)			
	Point Estimate		Monte Carlo Simulation	
	Per Patient	Per Patient per km	Per Patient	Per Patient per km
Naas	0.99 ± 0.21	1.24×10^{-2} $\pm 2.65 \times 10^{-3}$	0.993 ± 0.214	1.24×10^{-2} $\pm 2.67 \times 10^{-3}$
Mangweni	0.95 ± 0.23	1.24×10^{-2} $\pm 3.05 \times 10^{-3}$	0.953 ± 0.204	1.24×10^{-2} $\pm 2.66 \times 10^{-3}$
Mean	**0.97 ± 0.22**	**1.24×10^{-2}** **$\pm 2.85 \times 10^{-3}$**	**0.973 ± 0.209**	**1.24×10^{-2}** **$\pm 2.66 \times 10^{-3}$**

Table 5.20. Summary of transport costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling co-artemether as first-line agent. US$1.00 = ZAR 4.6072.

5.2.3. *Fixed Costs*

5.2.3.1. *Maintenance*

Clinic	Total Maintenance Cost (Per Patient) of Malaria in 1997 (Co-artemether) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	0.39 ± 0.06	$0.390 \pm 6.47 \times 10^{-2}$
Mangweni	0.41 ± 0.07	$0.390 \pm 6.44 \times 10^{-2}$
Mean Difference	**0.40 ± 0.06**	$0.390 \pm 6.46 \times 10^{-2}$

Table 5.21. Summary of maintenance costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling co-artemether as first-line agent. US$1.00 = ZAR 4.6072.

5.2.3.2. *Administrative & Support Staff Costs*

Clinic	Per-Patient Administrative & Support Staff Cost of Malaria in 1997 (Co-artemether) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	35.37 ± 6.64	35.44 ± 6.68
Mangweni	36.40 ± 6.65	35.37 ± 6.64
Mean	**35.88 ± 6.65**	**35.41 ± 6.66**

Table 5.22. Summary of administrative & support staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine and co-artemether as first-line agents. US$1.00 = ZAR 4.6072.

5.2.3.3. *Utilities*

Clinic	Per-Patient Utility Cost of Malaria in 1997 (Co-artemether) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	3.10 ± 0.48	3.11 ± 0.483
Mangweni	3.31 ± 0.48	3.10 ± 0.480
Mean	**3.20 ± 0.48**	**3.11 ± 0.482**

Table 5.23. Summary of utility costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine, artesunate and artesunate-mefloquine as first-line agents. US$1.00 = ZAR 4.6072.

5.2.4. *Total Costs for Co-artemether*

5.2.4.1. *Variable Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	**Monte Carlo Simulation**	**Point Estimate**	**Monte Carlo Simulation**
Drug Costs	191.24 ± 2.10	191.38 ± 1.49	185.83 ± 2.04	185.95 ± 1.41
Clinical Staff Costs	19.55 ± 6.12	19.57 ± 3.68	19.55 ± 6.12	19.48 ± 3.59
Consumables Costs	19.91 ± 2.60	21.19 ± 1.56	27.97 ± 2.60	29.22 ± 1.53
Transport Costs	0.99 ± 0.21	0.993 ± 0.214	0.95 ± 0.23	0.953 ± 0.204
Total	**228.71 ± 9.61**	**233.13 ± 6.94**	**234.30 ± 10.99**	**235.60 ± 6.73**

Table 5.24. Summary of variable costs at Naas and Mangweni Clinics in the event of co-artemether being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.2.4.2. *Fixed Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	**Monte Carlo Simulation**	**Point Estimate**	**Monte Carlo Simulation**
In-service Training	3.24	3.24*	3.05	3.05*
Maintenance	0.39 ± 0.06	0.390 ± 6.47×10^{-2}	0.41 ± 0.07	0.390 ± 6.44×10^{-2}
Administrative & Support Staff Costs	35.37 ± 6.64	35.44 ± 6.68	36.40 ± 6.65	35.37 ± 6.64
Utility Costs	3.10 ± 0.48	3.11 ± 0.483	3.31 ± 0.48	3.10 ± 0.480
Total	**42.10 ± 7.18**	**42.18 ± 7.23**	**43.17 ± 7.20**	**41.91 ± 7.18**

Table 5.25. Summary of fixed costs at Naas and Mangweni Clinics in the event of co-artemether being adopted as first-line therapy. US$1.00 = ZAR 4.6072. *Not simulated.

5.2.4.3. *Cost-effectiveness*

Clinic	Total Combined Fixed and Variable Cost per Patient	ACER
Naas	275.31 ± 13.79	1.669
Mangweni	277.51 ± 13.54	1.680
Mean	**276.41 ± 27.33** ***(US$ 59.98 ± US$ 5.93)***	**1.675**

Table 5.26. The cost-effectiveness of co-artemether at the study clinics in 1997, compared with chloroquine. A mean total cost per notified patient of R462.94 ± R102.45 (US$ 100.46 ± US$ 22.23) was used for the chloroquine, the baseline. US$1.00 = ZAR 4.6072.

5.3. Artesunate and Combinations

Three variations on artesunate treatment were examined: artesunate monotherapy, artesunate in combination with mefloquine, and artesunate in combination with sulfadoxine-pyrimethamine.

5.3.1. *Derivation of* R

Artesunate has been in almost constant use in Southeast Asia since the early 90s, with very little resistance thus far apparent. Resistance has been induced *in vitro*, but no reports of clinical resistance have appeared (WHO, 1998). Gay *et al* reported a single case of resistance to qinghaosu in West Africa in 1994. Furthermore, artesunate's gametocytocidal action may decrease incidence.

Considering the total absence of drug pressure in sub-Saharan Africa in general and South Africa in particular, and the non-emergence of resistance in areas of high drug pressure at the time of writing, R was taken to be zero in both mono- and combined therapy.

Furthermore, since there is no variation in R and R_{IV} is irrelevant, no risk analysis could be done.

5.3.2. *Variable Costs*

5.3.2.1. *Drug Costs*

Artesunate is not yet registered in South Africa, but is sold in Thailand at US$ 3.60 per 12 250mg tablets. This translates (at a mean 1997 US$/ZAR exchange rate of 4.6072) to R16.59 per 12 250mg tablets. Information supplied by the WHO suggests that the drug will be made available to Africa at 75¢ US (personal communication, M Gomes), but in the light of the Thailand experience, it was decided to use Thai prices as a guide.

Mefloquine is registered for malaria prophylaxis only. It is marketed as Lariam by Roche at R128.66 (US$ 27.92) per 8 250mg tablets. Costs of neuropsychiatric side effects incurred due to the use of mefloquine were not evaluated, though some risk of these is expected.

Artesunate monotherapy	Artesunate-mefloquine
4 mg/kg in a divided loading dose on day 1, followed by 2 mg/kg daily for 6 days	♦ 4 mg/kg artesunate daily for 3 days; ♦ 15-25 mg mefloquine base/kg as single/split dose on day 2 or 3
Artesunate-SP	
Adult	**Paediatric**
♦ 4 mg/kg artesunate daily for 3 days; ♦ 1500mg sulfadoxine + 75mg pyrimethamine as a single dose	♦ 4 mg/kg artesunate daily for 3 days; *Sulfadxoine-pyrimethamine:* ♦ < 1 yr: 125mg sulfadoxine + 6.25mg pyrimethamine single dose ♦ 1-3 yrs: 250mg sulfadoxine + 12.5mg pyrimethamine single dose ♦ 4-8 yrs: 500mg sulfadoxine + 25mg pyrimethamine single dose ♦ 9-14 yrs: 1000mg sulfadoxine + 50mg pyrimethamine single dose

Table 5.27. WHO recommended dosing schedule for artesunate and combinations.

Estimation of Drug Cost per Patient: Artesunate

Drug dosages, and hence costs, for patients of different ages and gender were estimated by means of the National Center for Health Statistics data used in the estimation of quinine dosage (see Section 5.2.2.3).

Clinic	**No. of Malaria Notifications in 1997**	**Total Artesunate Cost (ZAR)**	**Mean Artesunate cost per Patient (ZAR)**	**Total As-Mef Cost (ZAR)**	**Mean As-Mef cost per Patient (ZAR)**	**Total As-SP Cost (ZAR)**	**Mean As-SP cost per Patient (ZAR)**
Naas	236	1 092.46	4.63	12 443.65	52.73	4 612.80	19.55
Mangweni	271	1 218.97	4.50	13 841.95	51.08	5 093.57	18.80
Mean			**4.56** *(US$ 0.99)*		**51.90** *(US$ 11.26)*		**19.17** *(US$ 4.16)*

Table 5.28. Modelled cost of artesunate and artesunate-mefloquine first-line therapy at the study clinics in 1997. For mefloquine costs, a dose of 15 mg base/kg was used. US$1.00 = ZAR 4.6072.

Since R=0, no quinine drug costs were assumed to be incurred.

Summary

Clinic	**Total Drugs Cost (Per Patient) of Malaria in 1997 (Artesunate and combinations) (ZAR)**		
	Artesunate	**Artesunate-mefloquine**	**Artesunate-SP**
Naas	4.63	52.73	19.55
Mangweni	4.50	51.08	18.80
Mean	**4.56** *(US$ 0.99)*	**51.90** *(US$ 11.26)*	**19.17** *(US$ 4.16)*

Table 5.29. Summary of drug costs of malaria cases originating at Naas (236 cases) and Mangweni (271 cases) Clinics in 1997, modelling artesunate, artesunate-mefloquine and artesunate-SP as first-line agents. US$1.00 = ZAR 4.6072.

5.3.2.2. *Clinical Staff Costs*

Since R=0, no referrals are required, and therefore no hospital staff costs are incurred.

Clinic	**Resistance variable (1 + R)**	**Adjusted Number of Malaria Patients (n_{mi} x (1 + R))**	**Time per Consultation ($Time_{ci}$) (min)**	**Mean Salary per Minute (S_{mi}) (ZAR/min)**	**Total Clinical Staff Cost ($Cost_{CSi}$) (ZAR)**	**Clinical Staff Cost per Notified Patient ($Cost_{CSi}/n_{mi}$) (ZAR)**
Naas	1.0	236	10	0.471	1 112.21	4.71
Mangweni	1.0	271	10	0.471	1 277.16	4.71

Table 5.30. Clinical staff costs at Naas & Mangweni Clinics, assuming R=0.0, and using artesunate/artesunate-mefloquine as first-line therapy.

5.3.2.3. *Consumables*

Clinic	**Total Per-Patient Consumables Cost of Malaria in 1997 (Artesunate and combinations) (ZAR)**
	Point Estimates
Naas	14.43
Mangweni	22.49
Mean	**18.46**

Table 5.31. Summary of consumable costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using artesunate and artesunate combinations as first-line agents. US$1.00 = ZAR 4.6072.

5.3.2.4. *Transport*

$Cost_T$ may be estimated by the simple substitution of R. However, if R is zero, $Cost_T$ is also zero, since no patients need to be referred for hospitalisation.

5.3.3. *Fixed Costs*

5.3.3.1. *Maintenance*

Clinic	Total Maintenance Cost (Per Patient) of Malaria in 1997 (Artesunate and combinations) (ZAR)
	Point Estimate
Naas	8.94×10^{-2}
Mangweni	0.109
Mean	9.94×10^{-2}

Table 5.32. Summary of maintenance costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling atovaquone-proguanil as first-line agent. US$1.00 = ZAR 4.6072.

5.3.3.2. *Support & Administrative Staff Costs*

Clinic	Per-Patient Staff Time Cost of Malaria in 1997 (Artesunate and combinations) (ZAR)
	Point Estimate
Naas	4.37
Mangweni	5.35
Mean	4.86

Table 5.33. Summary of administrative & support staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and artesunate/artesunate-mefloquine as first-line agents. US$1.00 = ZAR 4.6072.

5.3.3.3. *Utilities*

Clinic	Per-Patient Utility Cost of Malaria in 1997 (Artesunate and combinations) (ZAR)
	Point Estimate
Naas	0.86
Mangweni	1.05
Mean	0.96

Table 5.34. Summary of utility costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine, artesunate and artesunate-mefloquine as first-line agents. US$1.00 = ZAR 4.6072.

5.3.4. *Total Costs for Artesunate and Artesunate Combinations*

5.3.4.1. *Variable Costs*

Category of Cost	Naas (ZAR)			Mangweni (ZAR)		
	As	**As-Mef**	**As-SP**	**As**	**As-Mef**	**As-SP**
Drug Costs	4.63	52.73	19.55	4.50	51.08	18.80
Clinical Staff Costs	3.65	3.65	3.65	3.65	3.65	3.65
Consumables Costs	14.43	14.43	14.43	22.49	22.49	22.49
Transport Costs	0.00	0.00	0.00	0.00	0.00	0.00
Total	22.71	70.81	37.63	30.64	77.22	44.94

Table 5.35. Summary of variable costs of artesunate alone and artesunate in combination with mefloquine and SP when used as first-line malaria treatment. US$1.00 = ZAR 4.6072.

5.3.4.2. *Fixed Costs*

Category of Cost	**Naas (ZAR)**			**Mangweni (ZAR)**		
	As	**As-Mef**	**As-SP**	**As**	**As-Mef**	**As-SP**
In-service Training	3.24	3.24	3.24	3.05	3.05	3.05
Maintenance	8.94×10^{2}	8.94×10^{2}	8.94×10^{-2}	0.109	0.109	0.109
Administrative & Support Staff Costs	4.37	4.37	4.37	5.35	5.35	5.35
Utility Costs	0.86	0.86	0.86	1.05	1.05	1.05
Total	8.56	8.56	8.56	9.56	9.56	9.56

Table 5.36. Summary of fixed costs of artesunate alone and artesunate in combination with mefloquine when used as first-line malaria treatment. US$1.00 = ZAR 4.6072.

5.3.4.3. *Cost-effectiveness*

Clinic	**Total Combined Fixed and Variable Cost per Patient**			**ACER**		
	As	**As-Mef**	**As-SP**	**As**	**As-Mef**	**As-SP**
Naas	31.27	79.37	46.19	14.70	5.790	9.948
Mangweni	40.20	86.78	54.50	11.60	5.374	8.557
Mean	**35.74** ***(US$ 7.76)***	**83.08** ***(US$ 18.03)***	**50.35** ***(US$ 10.93)***	**12.95**	**5.572**	**9.194**

Table 5.37. The cost-effectiveness of artesunate monotherapy and combinations at the study clinics in 1997, compared with chloroquine. A mean total cost per notified patient of R462.94 ± R102.45 was used for the chloroquine, the baseline. US$1.00 = ZAR 4.6072.

5.3.4.4. *Cost-effectiveness with Resistance and Increasing Drug Costs*

Adjustment	**Mean Total Combined Fixed and Variable Cost per Patient (ZAR)**			**ACER**		
	As	**As-Mef**	**As-SP**	**As**	**As-Mef**	**As-SP**
C_d x2	40.76	89.03	55.26	11.36	5.200	8.377
P_R=5%	81.34 ± 7.00	128.52 ± 7.20	96.02 ± 7.37	5.691	3.602	4.821
P_R=5%, C_d x2	85.33 ± 7.18	134.01 ± 7.08	99.90 ± 7.27	5.425	3.455	4.634
P_R=10%	125.43 ± 14.22	173.48 ± 14.59	140.81 ± 14.49	3.691	2.669	3.288
P_R=10%, C_d x2	131.39 ± 13.72	179.32 ± 14.19	144.92 ± 14.08	3.523	2.582	3.194

Table 5.38. The effect of increasing resistance and drug cost on the ACER for artesunate and its combinations. P_R = incidence of in vivo resistance; C_d = drug cost per patient. US$1.00 = ZAR 4.6072.

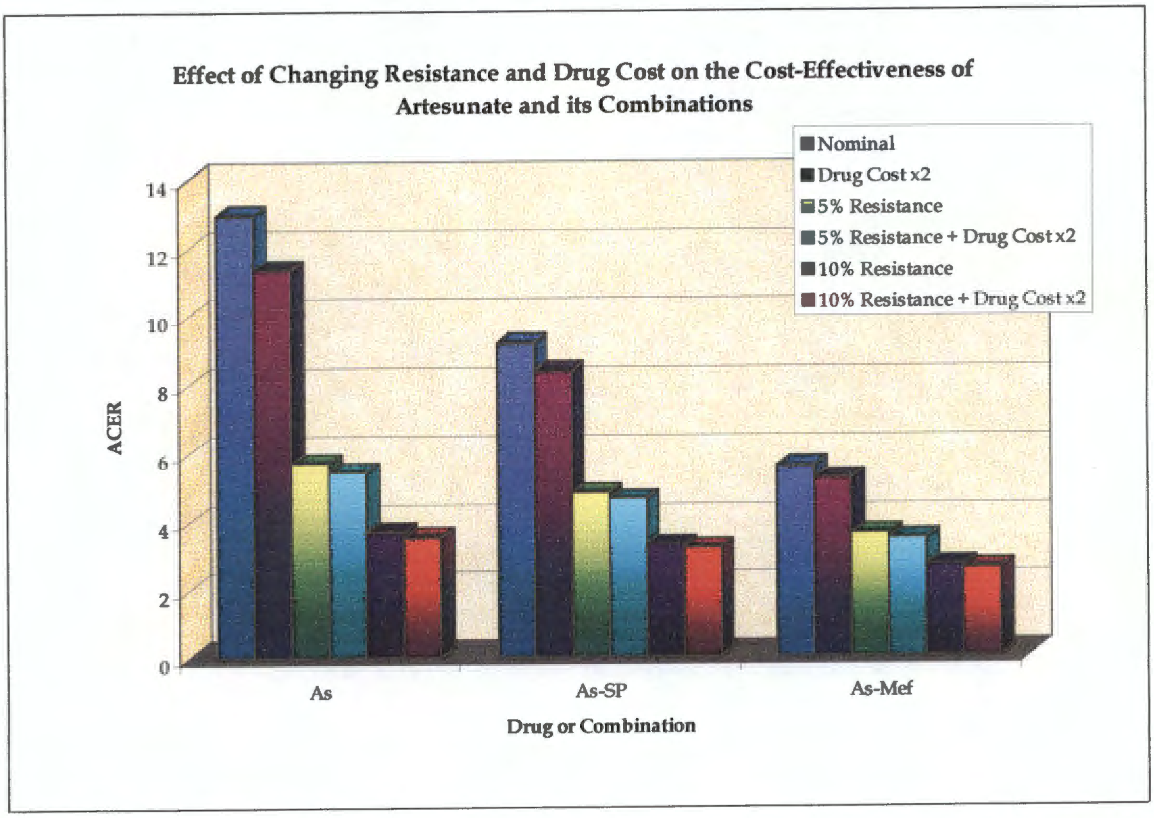

Figure 5.1. Increases in *in vivo* resistance levels have a profound effect on the cost-effectiveness of artesunate and its combinations. The effect of alterations of artesunate costs are less marked.

5.4. Atovaquone-proguanil

Radloff *et al* conducted a study in Lambaréné, Gabon in 1996 to test the efficacy of a novel combination of atovaquone and proguanil. 142 adult patients were randomly allocated either 1000mg atovaquone plus 400mg proguanil daily for 3 days, or amodiaquine 600mg on admission, 600mg at 24 hours, and 600mg at 48 hours. 126 of those patients were followed up until 28 days or recrudescence. Of 71 patients in the atovaquone-proguanil group, 62 (87.32%) were cured by day 28. Only 1 (1.41%) of the group recrudesced. However, 33% of the group complained of nausea, and 29% of vomiting. In contrast, the amodiaquine group showed a 71.83% cure rate (51 of 71 patients). The authors concluded that the atovaquone-proguanil combination was a safe, highly effective antimalarial therapy in Gabon.

A product monograph published by Glaxo Wellcome (Scott, 1998) claimed an overall efficacy of 99%, but this describes the results of trials conducted in South America, the Philippines, Southeast Asia, South America and Europe as well as Africa. The Lambaréné estimate of 87.32% is considered more valuable in the African context.

5.4.1. *Derivation of* R

The Gabon study carried out by Radloff *et al* in 1996 was chosen as the best indicator of resistance in sub-Saharan Africa. Their findings indicated an atovaquone-proguanil resistance prevalence of 12.676% in the region. Since very little work on atovaquone-proguanil has been done anywhere in the world, this was taken to be a fair estimate of resistance throughout the sub-continent.

Applying the principles developed in Section 5.2.1, R_{AP} was derived as follows:

$$R_{AP} = 0.1268 \times (0.7 \pm 0.15)$$
$$R_{AP} = 0.08876 \pm 0.01902$$

5.4.2. *Variable Costs*

5.4.2.1. *Drug Costs*

Assuming that the drugs would be made available to the Department of Health and Welfare at retail prices, atovaquone would be available as Wellvone (Glaxo Wellcome, R2 348.86 per 189 250mg tablets), and proguanil as Paludrine (Zeneca, R49.09 per 100 100mg tablets). If the combination were to be made available as Malarone (Glaxo Wellcome), the cost would be UK £21.00 per adult course (Medical Advisor for Infectious Diseases, Glaxo Wellcome South Africa). Using a mean 1997 UK Pound/South African Rand exchange rate of 7.550 (Olsen & Associates, http://www.oanda.com), this translates to R158.54 (US$ 34.40) per adult treatment course.

It was decided to base the estimation of costs on a Wellvone-Paludrine combination rather than Malarone, since the latter's price was only fixed very recently, and was estimated to be roughly equivalent in any event.

Adult	Paediatric
1000mg atovaquone + 400mg proguanil, one dose daily for 3 days	♦ 11-20kg: 250mg AQ + 100mg PG ♦ 21-30kg: 500mg AQ + 200mg PG ♦ 31-40kg: 750mg AQ + 300mg PG ♦ 41kg and over: 1000mg AQ + 400mg PG

Table 5.39. Dosing for atovaquone-proguanil (Lell *et al*, 1998; Radloff *et al*, 1996).

Estimation of Drug Cost per Patient: Atovaquone-proguanil

Drug dosages, and hence costs, for patients of different ages and gender were estimated by means of the National Center for Health Statistics data used in the estimation of quinine dosage (see Section 5.2.2.3).

Male				Female			
Age (yrs)	Est. Weight (kg)	Est. AP Dose (mg AQ/mg PG)	Est. Cost per Course (1997 ZAR)	Age (yrs)	Est. Weight (kg)	Est. AP Dose (mg AQ/mg PG)	Est. Cost per Course (1997 ZAR)
1-5	11-20	250/100	38.76	1-6	11-20	250/100	38.76
6-9	21-30	500/200	77.51	7-9	21-30	500/200	77.51
10-12	31-40	750/300	116.27	10-11	31-40	750/300	116.27
13+	41+	1000/400	155.02	12+	41+	1000/400	155.02

Table 5.40. Age/weight/dosage/cost relationships for paediatric treatment of malaria with atovaquone-proguanil. Atovaquone and proguanil costs are based upon December 1997 tender prices. US$1.00 = ZAR 4.6072.

Clinic	No. of Malaria Notifications in 1997	Total AP Cost (ZAR)	Mean AP cost per Patient (ZAR)
Naas	236	31508.78	133.51
Mangweni	271	34648.04	127.85
Mean			**130.49 *(US$ 28.32)***

Table 5.41. Modelled cost of atovaquone-proguanil first-line therapy at the study clinics in 1997. US$1.00 = ZAR 4.6072.

Estimation of Drug Cost per Patient: Quinine

Clinic	No. of patients in 1997	*R*	Est. no. of referrals	Cost to treat with IV Quinine (ZAR)		Cost to treat with PO Quinine (ZAR)	
				Per patient	**Adj. (Referrals x 0.7 ± 0.15)**	**Per patient**	**Adj. (Referrals x 0.3 ± 0.15)**
Naas	236	0.08876 ± 0.01902	20.95 ± 4.49	112.10	1643.74 ± 779.94	30.50	191.69 ± 157.44
						Total for Naas (IV + PO)	**1835.41 ± 937.38**
Mangweni	271	0.08876 ± 0.01902	24.05 ± 5.15	108.95	1834.48 ± 175.81	29.66	214.03 ± 175.81
						Total for Mangweni (IV + PO)	**2048.51 ± 1046.25**

Table 5.42. Calculation of quinine costs per clinic, assuming first-line drug is atovaquone-proguanil (R=0.08876 ± 0.01902). US$1.00 = ZAR 4.6072.

Summary

Study Clinic	Atovaquone-proguanil Cost (ZAR)		
	AP Cost	**Quinine Cost**	**Total Cost**
Naas	31 508.78	1 835.41 ± 937.38	33 344.19 ± 937.38
Mangweni	34 648.04	2 048.51 ± 1 046.25	36 696.55 ± 1 046.25

Table 5.43. Total projected 1997 drug costs for the treatment of patients originating at the study clinics; a comparison of chloroquine and atovaquone-proguanil. US$1.00 = ZAR 4.6072.

Clinic	Total Drugs Cost (Per Patient) of Malaria in 1997 (Atovaquone-proguanil) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	141.29 ± 3.97	141.59 ± 2.86
Mangweni	135.41 ± 3.86	135.62 ± 2.73
Mean	138.15 ± 3.91	138.61 ± 2.80

Table 5.44. Summary of drug costs of malaria cases originating at Naas (236 cases) and Mangweni (271 cases) Clinics in 1997, modelling atovaquone-proguanil as first-line agent. US$1.00 = ZAR 4.6072.

5.4.2.2. Consumables

Clinic	Total Consumables Cost (Per Patient) of Malaria in 1997 (Atovaquone-proguanil) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	24.80 ± 4.91	27.20 ± 2.91
Mangweni	32.86 ± 4.91	35.37 ± 2.91
Mean	**28.83 ± 2.24**	**31.29 ± 2.91**

Table 5.45. Summary of consumable costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling atovaquone-proguanil as first-line agent. US$1.00 = ZAR 4.6072.

5.4.2.3. Clinical Staff Costs

Clinic	Total Clinical Staff Cost (Per Patient) of Malaria in 1997 (Atovaquone-proguanil) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	32.80 ± 11.59	32.70 ± 6.76
Mangweni	32.80 ± 11.59	32.99 ± 6.83
Mean	**32.80 ± 11.59**	**32.85 ± 6.80**

Table 5.46. Summary of clinical staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling atovaquone-proguanil as first-line agent. US$1.00 = ZAR 4.6072.

5.4.2.4. *Transport*

$Cost_{TCQ}$ is R1671.74 ± R358.27 at Naas Clinic, R_{CQ}=0.34 ± 0.07, and R_{AP}=0.09 ± 0.02. Therefore, $Cost_{TAP}$ for Naas is R442.41 ± R94.80.

Similarly, $Cost_{TAP}$ for Mangweni Clinic was estimated to be R488.97 ± R104.78.

Clinic	Total Per-Patient Transport Costs of Malaria in 1997 (Atovaquone-proguanil) (ZAR/km)			
	Point Estimate		Monte Carlo Simulation	
	Per Patient	Per Patient per km	Per Patient	Per Patient per km
Naas	1.87 ± 0.40	2.34 x 10^{-2} ± 5.02 x 10^{-3}	1.88 ± 0.41	2.35 x 10^{-2} ± 5.14 x 10^{-3}
Mangweni	1.80 ± 0.44	2.34 x 10^{-2} ± 5.77 x 10^{-3}	1.82 ± 0.39	2.37 x 10^{-2} ± 5.04 x 10^{-3}
Mean	**1.84 ± 0.42**	**2.34 x 10^{-2} ± 5.39 x 10^{-3}**	**1.85 ± 0.40**	**2.36 x 10^{-2} ± 5.09 x 10^{-3}**

Table 5.47. Summary of transport costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling atovaquone-proguanil as first-line agent. US$1.00 = ZAR 4.6072.

5.4.3. *Fixed Costs*

5.4.3.1. *Maintenance*

Clinic	Total Maintenance Cost (Per Patient) of Malaria in 1997 (Atovaquone-proguanil) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	0.66 ± 0.12	0.66 ± 0.12
Mangweni	0.68 ± 0.12	0.66 ± 0.12
Mean Difference	0.67 ± 0.12	0.66 ± 0.12

Table 5.48. Summary of maintenance costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling atovaquone-proguanil as first-line agent. US$1.00 = ZAR 4.6072.

5.4.3.2. *Administrative & Support Staff*

Clinic	Per-Patient Staff Time Cost of Malaria in 1997 (Atovaquone-proguanil) (ZAR)	
	Point Estimate	**Monte Carlo Simulation**
Naas	63.00 ± 12.57	63.25 ± 12.83
Mangweni	64.06 ± 12.58	63.57 ± 12.58
Mean	**63.53 ± 12.57**	**126.82 ± 12.71**

Table 5.49. Summary of administrative & support staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling atovaquone-proguanil as first-line agent. US$1.00 = ZAR 4.6072.

5.4.3.3. *Utilities*

Clinic	Per-Patient Utility Cost of Malaria in 1997 (ZAR)	
	Point Estimate	**Monte Carlo Simulation**
Naas	5.10 ± 0.91	5.12 ± 0.93
Mangweni	5.31 ± 0.91	5.14 ± 0.91
Mean	**5.21 ± 0.91**	**5.13 ± 0.92**

Table 5.50. Summary of utility costs of malaria cases originating at Naas and Mangweni Clinics in 1997, comparing chloroquine and atovaquone-proguanil as first-line agents. US$1.00 = ZAR 4.6072.

5.4.4. *Total Costs for Atovaquone-proguanil*

5.4.4.1. *Variable Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	Monte Carlo Simulation	Point Estimate	Monte Carlo Simulation
Drug Costs	141.29 ± 3.97	141.59 ± 2.86	135.41 ± 3.86	135.62 ± 2.73
Clinical Staff Costs	32.80 ± 11.59	32.70 ± 6.76	32.80 ± 11.59	32.99 ± 6.83
Consumables Costs	24.80 ± 4.91	27.20 ± 2.91	32.86 ± 4.91	35.37 ± 2.91
Transport Costs	1.87 ± 0.40	1.88 ± 0.41	1.80 ± 0.44	1.82 ± 0.39
Total	**200.76 ± 20.87**	**203.37 ± 12.94**	**202.87 ± 20.80**	**205.80 ± 12.86**

Table 5.51. Summary of variable costs at Naas and Mangweni Clinics in the event of atovaquone-proguanil being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.4.4.2. *Fixed Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	Monte Carlo Simulation	Point Estimate	Monte Carlo Simulation
In-service Training	3.24	3.24*	3.05	3.05*
Maintenance	0.66 ± 0.12	0.66 ± 0.12	0.68 ± 0.12	0.66 ± 0.12
Administrative & Support Staff Costs	63.00 ± 12.57	63.25 ± 12.83	64.06 ± 12.58	63.57 ± 12.58
Utilities	5.10 ± 0.91	5.12 ± 0.93	5.31 ± 0.91	5.14 ± 0.91
Total	**72.00 ± 13.60**	**72.27 ± 13.88**	**73.10 ± 13.61**	**72.42 ± 13.61**

Table 5.52. Summary of fixed costs at Naas and Mangweni Clinics in the event of atovaquone-proguanil being adopted as first-line therapy. US$1.00 = ZAR 4.6072. *Not modelled.

5.4.4.3. *Cost-effectiveness*

Clinic	Total Combined Fixed and Variable Cost per Patient	ACER
Naas	275.64 ± 26.13	1.667
Mangweni	278.22 ± 25.72	1.676
Mean	**276.93 ± 25.93** ***(US$ 60.09 ± US$ 5.63)***	**1.672**

Table 5.53. The cost-effectiveness of amodiaquine at the study clinics in 1997, compared with chloroquine. A mean total cost per notified patient of R462.94 ± R102.45 was used for the chloroquine, the baseline. US$1.00 = ZAR 4.6072.

5.5. Halofantrine

Bouchaud *et al* published a study on the clinical efficacy and pharmacokinetics of micronized halofantrine in nonimmune patients in 1994. 28 malaria-infected individuals returning to Europe from sun-Saharan Africa were included in the study. 24 patients were cured after treatment with three doses of 250mg at 6-hour intervals. Of the remainder, 2 had subtherapeutic plasma concentrations due to poor absorption of the drug. Isolates from the other 2 showed halofantrine resistance *in vitro,* suggesting that drug resistance was repsonsible for the failure of treatment.

This study was chosen to provide an indicator of resistance because its patients were nonimmune, like the population found in South Africa's malarious regions, and because it took into account halofantrine's poor bioavailability.

5.5.1. *Derivation of R*

4 of the 28 patients studied by Bouchaud *et al* were not cured by treatment with halofantrine. This is a failure rate of 14.29%.

$$R_{HF} = 0.1429 \times (0.7 \pm 0.15)$$
$$R_{HF} = 0.1000 \pm 0.02144$$

5.5.2. *Variable Costs*

5.5.2.1. *Drug Costs*

Halofantrine is commercially available in South Africa as Halfan, marketed by SmithKline Beecham at R39.79 (US$ 8.63) per 6 250mg tablets.

Adult	Paediatric
500mg 6-hourly for 3 doses -- total 1500mg; repeated 7 days later.	Up to 40kg: 8 mg/kg 6-hourly for 3 doses -- total 24 mg/kg; repeated 7 days later.

Table 5.54. Dosing for halofantrine (SAMF, 1998).

Estimation of Drug Cost per Patient: Halofantrine

Drug dosages, and hence costs, for patients of different ages and gender were estimated by means of the National Center for Health Statistics data, as usual (see Section 5.2.2.3).

Clinic	No. of Malaria Notifications in 1997	Total HF Cost (ZAR)	Mean HF cost per Patient (ZAR)
Naas	236	15 549.55	65.89
Mangweni	271	17 159.74	63.32
Mean			**64.52 *(US$ 14.00)***

Table 5.55. Modelled cost of halofantrine first-line therapy at the study clinics in 1997. US$1.00 = ZAR 4.6072.

Estimation of Drug Cost per Patient: Quinine

Clinic	No. of patients in 1997	*R*	Est. no. of referrals	Cost to treat with IV Quinine (ZAR)		Cost to treat with PO Quinine (ZAR)	
				Per patient	Adj. (Referrals x 0.7 ± 0.15)	Per patient	Adj. (Referrals x 0.3 ± 0.15)
Naas	236	0.1000 ± 0.02144	23.60 ± 5.06	112.10	1851.89 ± 878.96	30.50	215.94 ± 177.42
						Total for Naas (IV + PO)	**2067.83 ± 1056.38**
Mangweni	271	0.1000 ± 0.02144	27.10 ± 5.81	108.95	2066.78 ± 980.95	29.66	241.14 ± 198.12
						Total for Mangweni (IV + PO)	**2307.92 ± 1179.07**

Table 5.56. Calculation of quinine costs per clinic, assuming first-line drug is halofantrine. US$1.00 = ZAR 4.6072.

Summary

Study Clinic	Halofantrine Cost (ZAR)		
	HF Cost	Quinine Cost	Total Cost
Naas	15 549.55	2 067.83 ± 1056.38	17 617.38 ± 1 056.38
Mangweni	17 159.74	2 307.92 ± 1179.07	19 467.66 ± 1 179.07

Table 5.57. Total projected 1997 drug costs for the treatment of patients originating at the study clinics; a comparison of chloroquine and halofantrine. US$1.00 = ZAR 4.6072.

Clinic	Total Drugs Cost (Per Patient) of Malaria in 1997 (Halofantrine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	74.65 ± 4.48	74.72 ± 3.02
Mangweni	71.84 ± 4.35	72.12 ± 3.10
Mean	**73.24 ± 4.41**	**73.42 ± 6.06**

Table 5.58. Summary of drug costs of malaria cases originating at Naas (236 cases) and Mangweni (271 cases) Clinics in 1997, modelling halofantrine as first-line agent. US$1.00 = ZAR 4.6072.

5.5.2.2. *Clinical Staff Costs*

Clinic	Total Clinical Staff Cost (Per Patient) of Malaria in 1997 (Halofantrine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	36.35 ± 13.06	35.82 ± 7.59
Mangweni	36.35 ± 13.06	36.27 ± 7.89
Mean	**36.35 ± 13.06**	**36.05 ± 7.74**

Table 5.59. Summary of clinical staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and halofantrine as first-line agents. US$1.00 = ZAR 4.6072.

5.5.2.3. *Consumables*

Clinic	Total Consumables Cost per Patient of Malaria in 1997 (Halofantrine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	26.11 ± 5.54	28.61 ± 3.21
Mangweni	34.17 ± 5.54	36.87 ± 3.37
Mean Difference	**30.14 ± 5.54**	**32.74 ± 3.29**

Table 5.60. Summary of consumable costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and halofantrine as first-line agents. US$1.00 = ZAR 4.6072.

5.5.2.4. *Transport*

$Cost_{TCQ}$ is R1 671.74 ± R358.27 at Naas Clinic, R_{CQ}=0.34 ± 0.07, and R_{HF}=0.10 ± 0.02. Therefore, $Cost_{THF}$ for Naas is R498.43 ± R106.86.

Similarly, $Cost_{THF}$ for Mangweni Clinic was estimated to be R550.89 ± R118.11.

Clinic	Total Per-Patient Transport Costs of Malaria in 1997 (Co-artemether) (ZAR/km)			
	Point Estimate		Monte Carlo Simulation	
	Per Patient	Per Patient per km	Per Patient	Per Patient per km
Naas	2.11 ± 0.45	2.64×10^{-2} $\pm 5.7 \times 10^{-3}$	2.09 ± 0.437	2.61×10^{-2} $\pm 5.47 \times 10^{-3}$
Mangweni	2.03 ± 0.50	2.64×10^{-2} $\pm 6.5 \times 10^{-3}$	2.04 ± 0.447	2.64×10^{-2} $\pm 5.81 \times 10^{-3}$
Mean	**2.07 ± 0.48**	2.64×10^{-2} $\pm 6.1 \times 10^{-3}$	**2.07 ± 0.442**	2.63×10^{-2} $\pm 5.64 \times 10^{-3}$

Table 5.61. Summary of transport costs of malaria cases originating at Naas and Mangweni Clinics in 1997, using chloroquine and atovaquone-proguanil as first-line agents. US$1.00 = ZAR 4.6072.

5.5.3. *Fixed Costs*

5.5.3.1. *Maintenance*

Clinic	Total Maintenance Cost (Per Patient) of Malaria in 1997 (Co-artemether) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	0.73 ± 0.14	0.722 ± 0.132
Mangweni	0.75 ± 0.14	0.730 ± 0.141
Mean	**0.74 ± 0.14**	**0.726 ± 0.137**

Table 5.62. Summary of maintenance costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling halofantrine as first-line agent. US$1.00 = ZAR 4.6072.

5.5.3.2. *Administrative & Support Staff Costs*

Clinic	Per-Patient Staff Time Cost of Malaria in 1997 (Halofantrine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	70.42 ± 14.16	69.62 ± 13.65
Mangweni	71.48 ± 14.18	70.48 ± 14.51
Mean	70.95 ± 14.17	70.05 ± 14.08

Table 5.63. Summary of administrative & support staff costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling halofantrine as first-line agent. US$1.00 = ZAR 4.6072.

5.5.3.3. *Utilities*

Clinic	Per-Patient Utility Cost of Malaria in 1997 (Halofantrine) (ZAR)	
	Point Estimate	Monte Carlo Simulation
Naas	5.64 ± 1.02	5.58 ± 0.987
Mangweni	5.85 ± 1.03	5.64 ± 1.04
Mean	5.74 ± 1.03	5.61 ± 1.01

Table 5.64. Summary of utility costs of malaria cases originating at Naas and Mangweni Clinics in 1997, modelling halofantrine as first-line agent. US$1.00 = ZAR 4.6072.

5.5.4. *Total Costs for Halofantrine*

5.5.4.1. *Variable Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	Monte Carlo Simulation	Point Estimate	Monte Carlo Simulation
Drug Costs	74.65 ± 4.48	74.72 ± 3.02	71.84 ± 4.35	72.12 ± 3.10
Clinical Staff Costs	36.35 ± 13.06	35.82 ± 7.59	36.35 ± 13.06	36.27 ± 7.89
Consumables Costs	26.11 ± 5.54	28.61 ± 3.21	34.17 ± 5.54	36.87 ± 3.37
Transport Costs	2.11 ± 0.45	2.09 ± 0.437	2.03 ± 0.50	2.04 ± 0.447
Total	**139.22 ± 23.53**	**141.24 ± 14.26**	**144.39 ± 23.45**	**147.30 ± 14.81**

Table 5.65. Summary of variable costs at Naas and Mangweni Clinics in the event of halofantrine being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.5.4.2. *Fixed Costs*

Category of Cost	Naas (Per Patient) (ZAR)		Mangweni (Per Patient) (ZAR)	
	Point Estimate	Monte Carlo Simulation	Point Estimate	Monte Carlo Simulation
In-service Training	3.24	3.24*	3.05	3.05*
Maintenance	0.73 ± 0.14	0.722 ± 0.132	0.75 ± 0.14	0.730 ± 0.141
Administrative & Support Staff Costs	70.42 ± 14.16	69.62 ± 13.65	71.48 ± 14.18	70.48 ± 14.51
Utility Costs	5.64 ± 1.02	5.58 ± 0.987	5.85 ± 1.03	5.64 ± 1.04
Total	**80.03 ± 15.32**	**79.16 ± 14.77**	**81.13 ± 15.35**	**79.90 ± 15.69**

Table 5.66. Summary of fixed costs at Naas and Mangweni Clinics in the event of halofantrine being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.5.4.3. *Cost-effectiveness*

Clinic	Total Combined Fixed and Variable Cost per Patient	ACER
Naas	220.40 ± 28.24	2.085
Mangweni	227.20 ± 29.79	2.053
Mean	**223.80 ± 29.02** ***(US$ 48.56 ± US$ 6.30)***	**2.069**

Table 5.67. The cost-effectiveness of halofantrine at the study clinics in 1997, compared with chloroquine. A mean total cost per notified patient of R462.94 ± R102.45 was used for the chloroquine, the baseline. US$1.00 = ZAR 4.6072.

5.6. Mefloquine

Resistance to mefloquine in the study region had not appeared by 1990 (Freese *et al*, 1994), and was still absent in isolates tested *in vitro* in 1994 (Deacon *et al*, 1994). However, since its deployment for the first-line treatment of *P. falciparum* infections in Thailand in the mid-Eighties, antimalarial cure rates for the organism in the region declined from nearly 100% at the time of introduction to 50% by 1992 (White, 1992).

Other studies conducted in sub-Saharan Africa on the efficacy of treatment with mefloquine (Del Nero *et al*, 1993; Del Nero *et al*, 1994; Okoyeh *et al*, 1997) indicate that resistance has not yet become a problem in the region.

5.6.1. *Derivation of* R

Mefloquine has been used extensively in Southeast Asia, but has had little exposure in sub-Saharan Africa. This fact, combined with the evidence of mefloquine sensitivity in the study region published by Freese *et al* and Deacon *et al*, allows the assumption that *in vivo* resistance to mefloquine in the Shongwe and Tonga districts is not significantly different from nil. Hence, R=0.

5.6.2. *Variable Costs*

5.6.2.1. *Drug Costs*

The WHO recommends a dosage regimen of 25 mg mefloquine base per kilogram, not exceeding 1 500 mg, spread over 2-3 days. Mefloquine is marketed in South Africa as Lariam, which sells for R128.66 per package of 8 250mg tablets. This equates to R0.064 per milligram.

Estimation of Drug Cost per Patient: Mefloquine

Using the National Center for Health Statistics tables for gauging age/weight/dosage relationships, assuming a mean adult weight of 70 kg, and using standard dosage of 25 mg/kg, an adult course was estimated to cost R96.50 (using the full dose of 1 500mg).

Clinic	No. of Malaria Notifications in 1997	Total Mef Cost (ZAR)	Mean MEF cost per Patient (ZAR)
Naas	236	18 271.65	77.42
Mangweni	271	20 245.94	74.71
Mean			**76.07 *(US$ 16.51)***

Table 5.68. Modelled cost of mefloquine first-line therapy at the study clinics in 1997. US$1.00 = ZAR 4.6072.

Summary

Clinic	Total Drugs Cost (Per Patient) of Malaria in 1997 (Mefloquine) (ZAR)
	Point Estimate
Naas	77.42
Mangweni	74.71
Mean	**76.07**

Table 5.69. Summary of drug costs of malaria cases originating at Naas (236 cases) and Mangweni (271 cases) Clinics in 1997, modelling mefloquine as first-line agent. US$1.00 = ZAR 4.6072.

5.6.3. *Other Costs*

Since $R=0$, all other fixed and variable costs were identical to those calculated for artesunate and its combinations in section 6.3.

5.6.4. *Total Costs for Mefloquine*

5.6.4.1. *Variable Costs*

Category of Cost	**Naas (Per Patient) (ZAR)**	**Mangweni (Per Patient) (ZAR)**
	Point Estimate	**Point Estimate**
Drug Costs	77.42	74.71
Clinical Staff Costs	3.65	3.65
Consumables Costs	14.43	22.49
Transport Costs	0.00	0.00
Total	**95.50**	**100.85**

Table 5.70. Summary of variable costs at Naas and Mangweni Clinics in the event of mefloquine being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.6.4.2. Fixed Costs

Category of Cost	**Naas (Per Patient) (ZAR)**	**Mangweni (Per Patient) (ZAR)**
	Point Estimate	**Point Estimate**
In-service Training	3.24	3.05
Maintenance	8.94×10^{-2}	0.109
Administrative & Support Staff Costs	4.37	5.35
Utility Costs	0.86	1.05
Total	**8.56**	**9.56**

Table 5.71. Summary of fixed costs at Naas and Mangweni Clinics in the event of mefloquine being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.6.4.3. Cost-effectiveness

Clinic	**Total Combined Fixed and Variable Cost per Patient**	**ACER**
Naas	104.06	4.416
Mangweni	110.41	4.224
Mean	**107.24** *(US$ 23.27)*	**4.317**

Table 5.72. The cost-effectiveness of mefloquine at the study clinics in 1997, compared with chloroquine. A mean total cost per notified patient of R462.94 ± R102.45 was used for the chloroquine, the baseline. US$1.00 = ZAR 4.6072.

5.6.4.4. Cost-effectiveness at 10% Resistance

Clinic	Total Combined Fixed and Variable Cost per Patient	ACER
Naas	183.48 ± 20.46	2.504
Mangweni	188.54 ± 19.61	2.473
Mean	186.01 ± 20.04	2.489

Table 5.73. Using an arbitrary *in vivo* drug resistance level of 10%, a risk simulation was run to determine the effect of an increased rate of resistance on the ACER. The result is a 42.34% drop in cost-effectiveness with respect to chloroquine. US$1.00 = ZAR 4.6072.

5.7. Pyronaridine

Two studies conducted in Yaoundé, Cameroon (Ringwald *et al*, 1996; Ringwald *et al*, 1998) found no resistance to pyronaridine in *P. falciparum in vivo* using a total dose of 32 mg/kg over 3 days. In contrast, a Thai study found 12% resistance (3 of 26) using a total dose of 1 800 mg over 5 days, which, using a mean adult body weight of 70 kg, is equivalent to 25.7 mg/kg (Looareesuwan *et al*, 1996).

Pyronaridine has not been used on a large scale in sub-Saharan Africa, while it has been employed in Southeast Asia for some time. Also, the dosages used in the Thai study were lower than those used by Ringwald *et al*. For these reasons it was decided to accept the Yaoundé findings of zero resistance *in vivo* in sub-Saharan Africa.

5.7.1. Derivation of R

Pyronaridine has not been used on a large scale in sub-Saharan Africa, while it has been employed in Southeast Asia for some time. Also, the dosages used in the Thai study were lower than those used by Ringwald *et al*. For these reasons it was decided to accept the Yaoundé findings of zero resistance *in vivo* in sub-Saharan Africa; R=0.0.

5.7.2. *Variable Costs*

5.7.2.1. Drug Costs

The final recommended cost of an adult treatment course of pyronaridine has not yet been confirmed, but the WHO target cost for sub-Saharan Africa is US$ 1.00, or R4.61, using a mean 1997 exchange rate of 4.60720 Rands to the dollar (personal communication, Dr T Kanyok, WHO pyronaridine manager). Due to South Africa's perceived 'richer' status in Africa and the uncertainty in the price at which the drug might be made available, it was decided to use the cost of $3.00 (R13.82) per adult course quoted by Winstanley in 1996.

Factors which will determine cost include the price at which industry can manufacture and commercialise the drug within Africa (including synthesis, finished product production, recoup of R&D and registration costs, distribution costs, wholesaler mark-up, and final price to the patient from point of local distribution). Some savings will probably be realised if the drug is made available directly to the Department of Health. Also critical will be the length and dose of an adult treatment course. WHO presently envisions this to be either 6 or 12 mg/kg/day for 3 days (T Kanyok).

For the purposes of this study, using the evidence from Yaoundé and Thailand, it was decided to use a dose of 12 mg/kg per day for 3 days for all estimations of costs.

Estimation of Drug Cost per Patient: Pyronaridine

National Center for Health Statistics data was once again used for the estimation of age/weight/dosage relationships. Assuming mean adult weight to be 70 kg, and standard dosage to be 36 mg/kg spread over 3 days, the cost of a pyronaridine course is R0.55 (US$ 0.12) per kg.

Clinic	No. of Malaria Notifications in 1997	Total PN Cost (ZAR)	Mean PN cost per Patient (ZAR)
Naas	236	2 438.07	10.33
Mangweni	271	2 720.41	10.04
Mean			**10.19 *(US$ 2.21)***

Table 5.74. Modelled cost of pyronaridine first-line therapy at the study clinics in 1997. US$1.00 = ZAR 4.6072.

Since $R=0$, no quinine drug costs were assumed to be incurred.

5.7.3. *Other Costs*

As in the case of mefloquine, other variable and fixed costs are identical to those calculated in section 6.3 for artesunate and its derivatives.

5.7.4. *Total Costs for Pyronaridine*

5.7.4.1. *Variable Costs*

Category of Cost	**Naas (Per Patient) (ZAR)**	**Mangweni (Per Patient) (ZAR)**
	Point Estimate	**Point Estimate**
Drug Costs	10.33	10.04
Clinical Staff Costs	3.65	3.65
Consumables Costs	14.43	22.49
Transport Costs	0.00	0.00
Total	**28.41**	**36.18**

Table 5.75. Summary of variable costs at Naas and Mangweni Clinics in the event of pyronaridine being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.7.4.2. *Fixed Costs*

Category of Cost	**Naas (Per Patient) (ZAR)**	**Mangweni (Per Patient) (ZAR)**
	Point Estimate	**Point Estimate**
In-service Training	3.24	3.05
Maintenance	8.94×10^{-2}	0.109
Administrative & Support Staff Costs	4.37	5.35
Utility Costs	0.86	1.05
Total	**8.56**	**9.56**

Table 5.76. Summary of fixed costs at Naas and Mangweni Clinics in the event of pyronaridine being adopted as first-line therapy. US$1.00 = ZAR 4.6072.

5.7.4.3. *Cost-effectiveness*

Clinic	**Total Combined Fixed and Variable Cost per Patient**	**ACER**
Naas	36.97	12.43
Mangweni	45.74	10.20
Mean	**41.36 *(US$ 8.98)***	**11.19**

Table 5.77. The cost-effectiveness of pyronaridine at the study clinics in 1997, compared with chloroquine. A mean total cost per notified patient of R462.94 ± R102.45 was used for the chloroquine, the baseline. US$1.00 = ZAR 4.6072.

5.7.4.4. *Cost-effectiveness with Resistance and Increased Drug Cost*

Adjustment	Mean Combined Total Variable and Fixed Cost per Patient (ZAR)	ACER
C_d x2	52.01	8.901
$P_R = 5\%$	83.25 ± 10.32	5.561
$P_R = 5\%$, C_d x2	97.36 ± 7.28	4.755
$P_R = 10\%$	128.83 ± 20.35	3.598
$P_R = 10\%$, C_d x2	142.49 ± 14.76	3.249

Table 5.78. The effect on the ACER of increasing resistance rate and drug cost in pyronaridine.

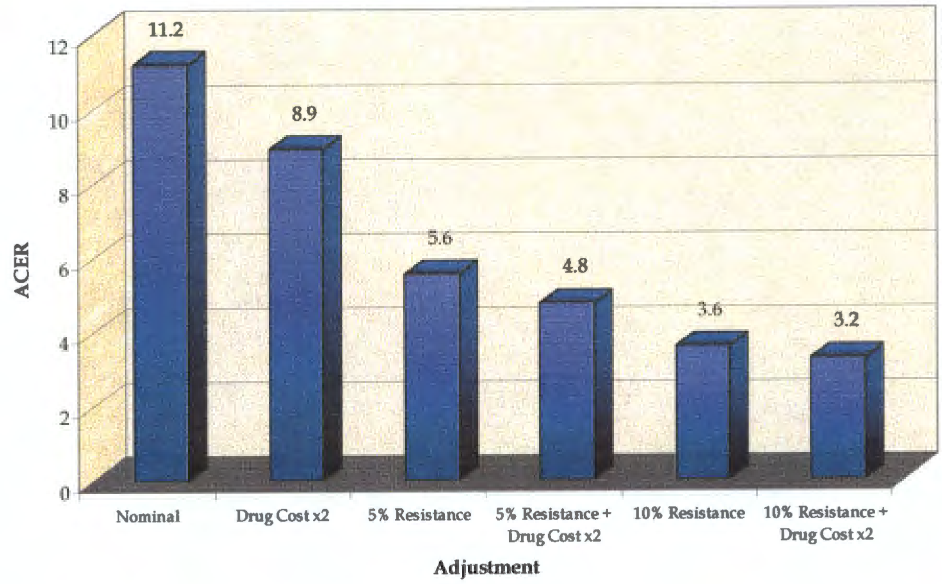

Figure 5.2. Increasing resistance substantially affects cost-effectiveness of modelled drugs, for example pyronaridine above. Drug costs play a lesser role.

5.8. Comparisons Between Drug Models

5.8.1. *Summary of Results*

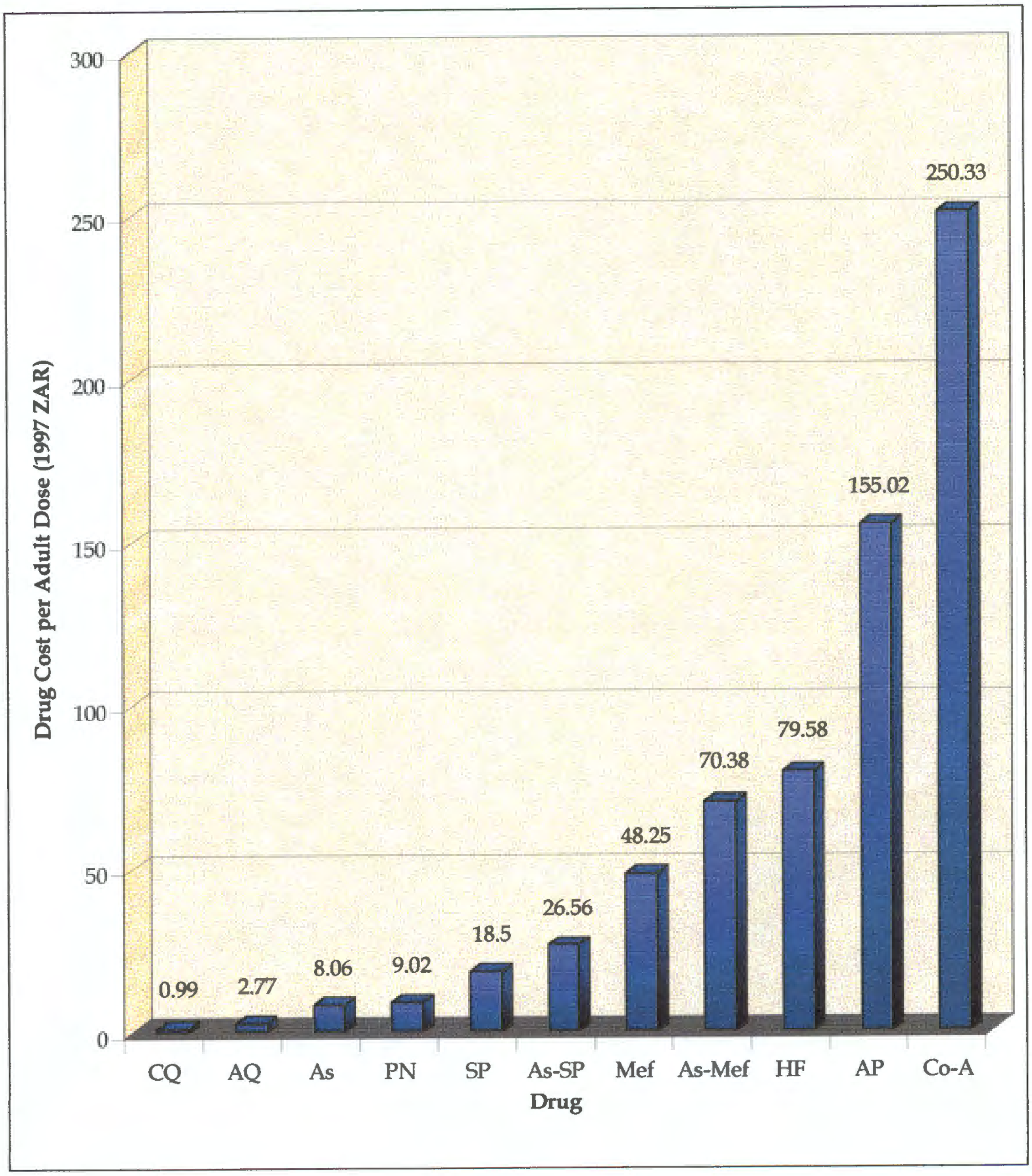

Figure 5.3. 1997 drug costs. As=artesunate; PN=pyronaridine; SP=sulfadoxine-pyrimethamine; AM=artesunate-mefloquine; Mef=mefloquine; HF=halofantrine; AQ=amodiaquine; CQ=chloroquine; AP=atovaquone-proguanil; Co-A=co-artemether.

Drug	Cost per Patient of Notifications Arising at Naas Clinic (1997 ZAR)			Cost per Patient of Notifications Arising at Mangweni Clinic (1997 ZAR)			Mean Total Cost (1997 ZAR)
	Variable Costs	Fixed Costs	Total Costs	Variable Costs	Fixed Costs	Total Costs	
CQ	213.51 ± 49.73	248.41 ± 50.96	461.92 ± 100.69	217.83 ± 50.97	246.11 ± 53.23	463.94 ± 104.20	**462.94 ± 102.45**
SP	56.14 ± 5.97	35.95 ± 6.15	92.09± 12.12	63.56 ± 5.62	36.02 ± 5.97	99.58 ± 5.80	**95.86 ± 11.86**
AQ	169.43 ± 38.40	193.30 ± 40.42	362.73 ± 78.82	175.86 ± 39.48	192.65 ± 41.55	368.51 ± 81.03	**365.62 ± 79.93**
As*	22.71	8.56	31.27	30.64	9.56	40.20	**35.74**
As-Mef*	70.81	8.56	79.37	77.22	9.56	86.78	**83.08**
As-SP*	37.63	8.56	46.19	44.94	9.56	54.50	**50.35**
AP	203.37 ± 12.94	72.27 ± 13.88	275.64 ± 26.13	205.80 ± 12.86	72.42 ± 13.61	278.22 ± 25.72	**276.93 ± 25.93**
Co-A*	233.13 ± 6.94	42.18 ± 7.23	275.31 ± 13.79	235.60 ± 6.73	41.91 ± 7.18	277.51 ± 13.54	**276.41 ± 27.33**
HF	141.24 ± 14.26	79.16 ± 14.77	220.40 ± 28.24	147.30 ± 14.81	79.90 ± 15.69	227.20 ± 29.79	**223.80 ± 29.02**
Mef	95.50	8.56	104.06	100.85	9.56	110.41	**107.24**
PN*	28.41	8.56	36.97	36.18	9.56	45.74	**41.36**

Table 5.79. Summary of modelled costs per notified malaria patient cured for each studied drug. *Drug costs in South Africa unconfirmed at the time of writing. US$1.00 = ZAR 4.6072.

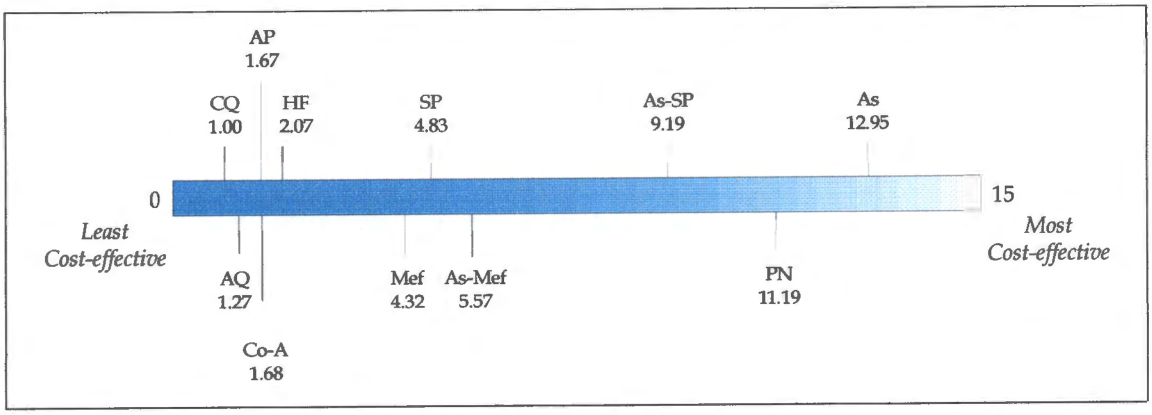

Figure 5.4. Rankings of drugs according to modelled cost-effectiveness. CQ = chloroquine; AQ = amodiaquine; AP = atovaquone-proguanil; Co-A = co-artemether; HF = halofantrine; Mef = mefloquine; SP = sulfadoxine-pyrimethamine; As-Mef = artesunate/mefloquine; As-SP = artesunate/sulfadoxine-pyrimethamine; PN = pyronaridine; As = artesunate.

Drug	**Average Cost-Effectiveness Ratio (ACER)**
Chloroquine	**1.0**
Sulfadoxine-pyrimethamine	**4.8**
Amodiaquine	**1.3**
Artesunate*	**13.0**
Artesunate-mefloquine*	**5.6**
Artesunate-SP*	**9.2**
Atovaquone-proguanil	**1.7**
Co-artemether	**1.7**
Halofantrine	**2.1**
Mefloquine	**4.3**
Pyronaridine*	**11.2**

Table 5.80. Summary of cost-effectiveness results. * Drug prices for Africa are not yet known with certainty.

Artesunate and pyronaridine (with ACERs of 12.95 and 12.76 respectively, when compared to chloroquine) emerged as the most cost-effective monotherapeutic options, although in both cases South African prices were estimated from WHO recommendations and international prices, and could not be confirmed.

Of the combinations, artesunate-SP proved the most cost-effective, with an ACER of 9.194 with respect to chloroquine. Halofantrine, atovaquone-proguanil, and co-artemether were relatively non-cost-effective due to their high cost, which negated any advantage that might have been given by lower incidence of *in vivo* resistance. Amodiaquine and chloroquine were the least cost-effective, because of the effect of high resistance.

There was a significant correlation between resistance rate and ACER (Spearman r = -0.8963, P = 0.0004), but no significant relationship was found between ACER and drug cost (Spearman r = -0.03646, P = 0.9241).

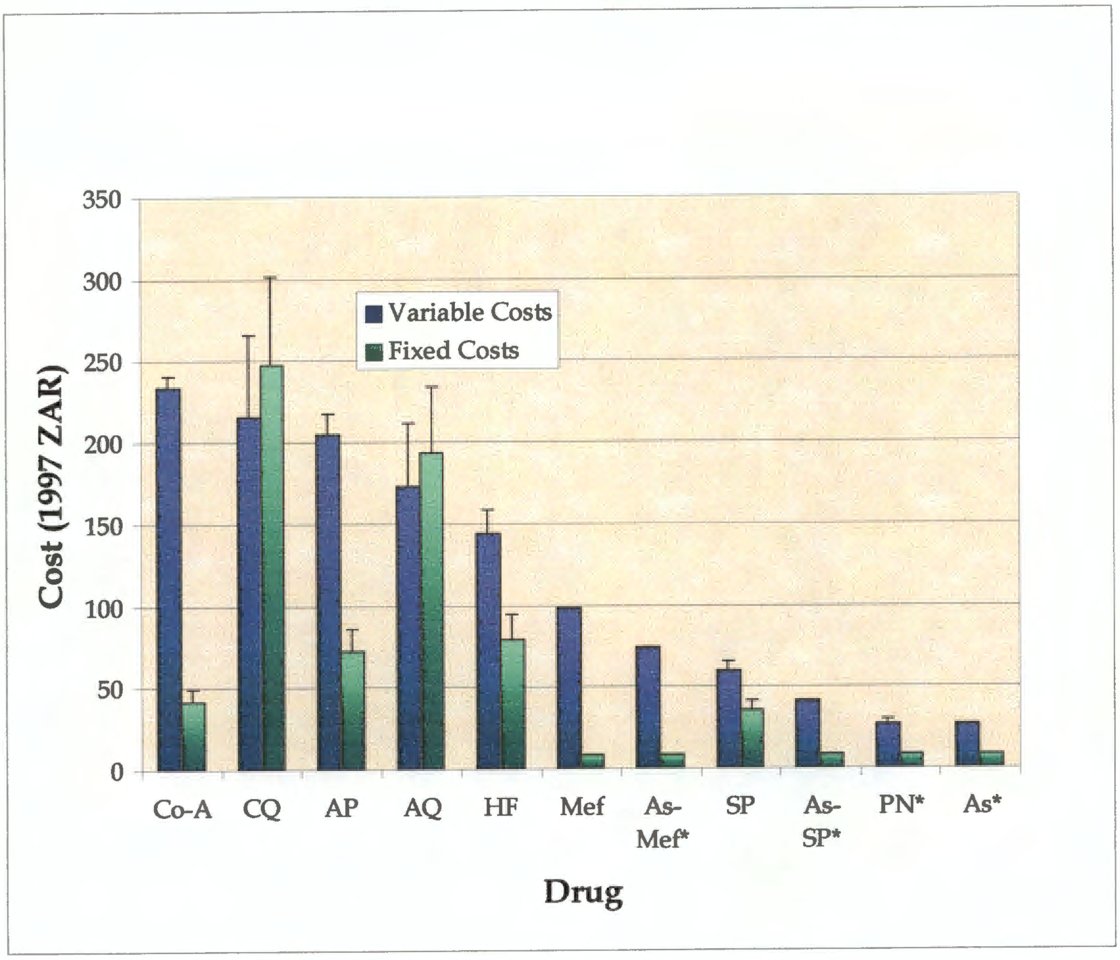

Figure 5.5. Comparison of cost per notified patient of modelled antimalarial drugs. Co-A = co-artemether; CQ = chloroquine; AP = atovaquone-proguanil; AQ = amodiaquine; HF = halofantrine; Mef = mefloquine; As-Mef = artesunate/mefloquine; SP = sulfadoxine-pyrimethamine; As-SP = artesunate/sulfadoxine-pyrimethamine; PN = pyronaridine; As = artesunate.

* Drug prices for Africa are not yet known with certainty.

5.8.2. *Clinic Visits and Patient Days*

Drug	**Naas**		**Mangweni**	
	Additional Clinic Visits	**Hospital Patient Days**	**Additional Clinic Visits**	**Hospital Patient Days**
Chloroquine	79.15 ± 16.96	237.45 ± 50.88	90.89 ± 19.48	272.67 ± 58.44
Sulfadoxine-pyrimethamine	9.09 ± 1.96	27.26 ± 5.88	10.43 ± 2.25	31.30 ± 6.75
Amodiaquine	60.77 ± 13.02	182.31 ± 39.06	69.78 ± 14.96	209.34 ± 44.88
Co-artemether	11.07 ± 2.37	33.21 ± 7.11	12.71 ± 2.72	38.13 ± 8.16
Artesunate	0.00	0.00	0.00	0.00
Artesunate-mefloquine	0.00	0.00	0.00	0.00
Artesunate-SP	0.00	0.00	0.00	0.00
Atovaquone-proguanil	20.95 ± 4.49	62.85 ± 13.47	24.05 ± 5.15	72.15 ± 15.45
Halofantrine	23.60 ± 5.06	70.80 ± 15.18	27.10 ± 5.81	81.30 ± 17.43
Mefloquine	0.00	0.00	0.00	0.00
Pyronaridine	0.00	0.00	0.00	0.00

Table 5.81. Comparitive benefits between the drugs studied. Hospitalised patients were assumed to remain at the hospital for an average of 3 days.

Relative benefit ratios were calculated for the study drugs, in terms of the proportion of clinic visits averted and hospital patient days saved. Relative benefit ratio is inversely proportional to *in vivo* resistance.

Drug	Average Benefits Ratio
Chloroquine	1.000
Sulfadoxine-pyrimethamine	8.711
Amodiaquine	1.302
Co-artemether	7.151
Artesunate	Unquantifiable*
Artesunate-mefloquine	Unquantifiable*
Artesunate-SP	Unquantifiable*
Atovaquone-proguanil	3.779
Halofantrine	3.354
Mefloquine	Unquantifiable*
Pyronaridine	Unquantifiable*

Table 5.82. Average benefits ratios of the study drugs, comparing benefits in terms of clinic visits and hospital patient days saved. *Since resistance for artesunate, mefloquine and pyronaridine was modelled as zero, the average benefits ratio was taken to unquantifiably large.

5.8.3. *African Drug Prices*

Drug prices from Kenya and Uganda were obtained, and their effect on cost-effectiveness were evaluated.

5.8.3.1. *Kenya*

Drug	Cost per Treatment Course (Kenyan Shillings)	Cost per Adult Treatment Course (ZAR)	ACER with Kenyan Cost
Chloroquine*	10.00	0.788	1.031
Sulfadoxine-pyrimethamine*	50.00 - 75.00	3.941 - 5.912	5.606 - 5.502
Quinine (Oral)	180.00	14.189	N/A
Artesunate (7 d)	200.00	15.766	10.70

Table 5.83. Comparison of drug prices in Kenya and South Africa in 1997, and the effect of using to Kenyan prices to calculate ACERs. The Kenyan prices were provided by F ter Kuile & J Alaii, and converted to South African Rands using a conversion rate of 12.686 KSh to the Rand (mean 1997 exchange rate, Olsen and Associates, www.oanda.com). All ACERs were calculated using South African chloroquine costs as a comparator.

***Indicates use of Kenyan quinine prices in calculation. Since there is assumed to be no resistance to artesunate, quinine is not incorporated in the artesunate drug model.**

5.8.3.2. *Uganda*

Drug	Cost per Treatment Course (Ugandan Shillings)	Cost per Adult Treatment Course (ZAR)	ACER with Ugandan Cost
Sulfadoxine-pyrimethamine	500 - 3 000	2.149 - 12.894	5.596 - 5.072
Artesunate (7 d)	16 000	25.789	9.142

Table 5.84. Comparison of drug prices in Uganda and South Africa in 1997, and the effect of using to Ugandan prices to calculate ACERs. The Ugandan prices were provided by M Willcox, and converted to South African Rands using a conversion rate of 232.661 USh to the Rand (mean 1997 exchange rate, Olsen and Associates, www.oanda.com).

In both cases, drug prices tended to vary considerably depending on the region of the country in which they were sold, the source of drug supply, competition between resellers, and ability to pay (personal communication, M Willcox).

5.8.4. *Curve Fitting*

The model generates data lying along a curve described by the following equation:

$$y = Span1 \cdot e^{-K_1 x} + Span2 \cdot e^{-K_2 x} + Plateau \qquad (20)$$

This expression describes two-phase exponential decay, and fits the model exactly (R^2 = 1.000). Each modelled drug has its own unique values for *Span*1, *Span*2, K_1, K_2, and *Plateau*. x is resistance prevalence, and y is the ACER at resistance x. K_1 and K_2 are rate constants. The two phases implicit in the equation describe the patient return rate, and the ratio of patients treated with oral versus intravenous quinine upon admission to hospital, respectively. *Span*1 and *Span*2 are constants relating to these. *Plateau* is the lowest possible value of the ACER, according to the model. Appendix C contains a table of values for *Span*1, *Span*2, K_1, K_2 and *Plateau* for each modelled drug.

5.8.5. *Critical Values for Resistance Prevalence*

Critical values of resistance prevalence for drugs were calculated to determine the levels of resistance at which one drug might become more or less cost-effective than another. These figures are not generalisable outside of South Africa, as they are based on South African costs.

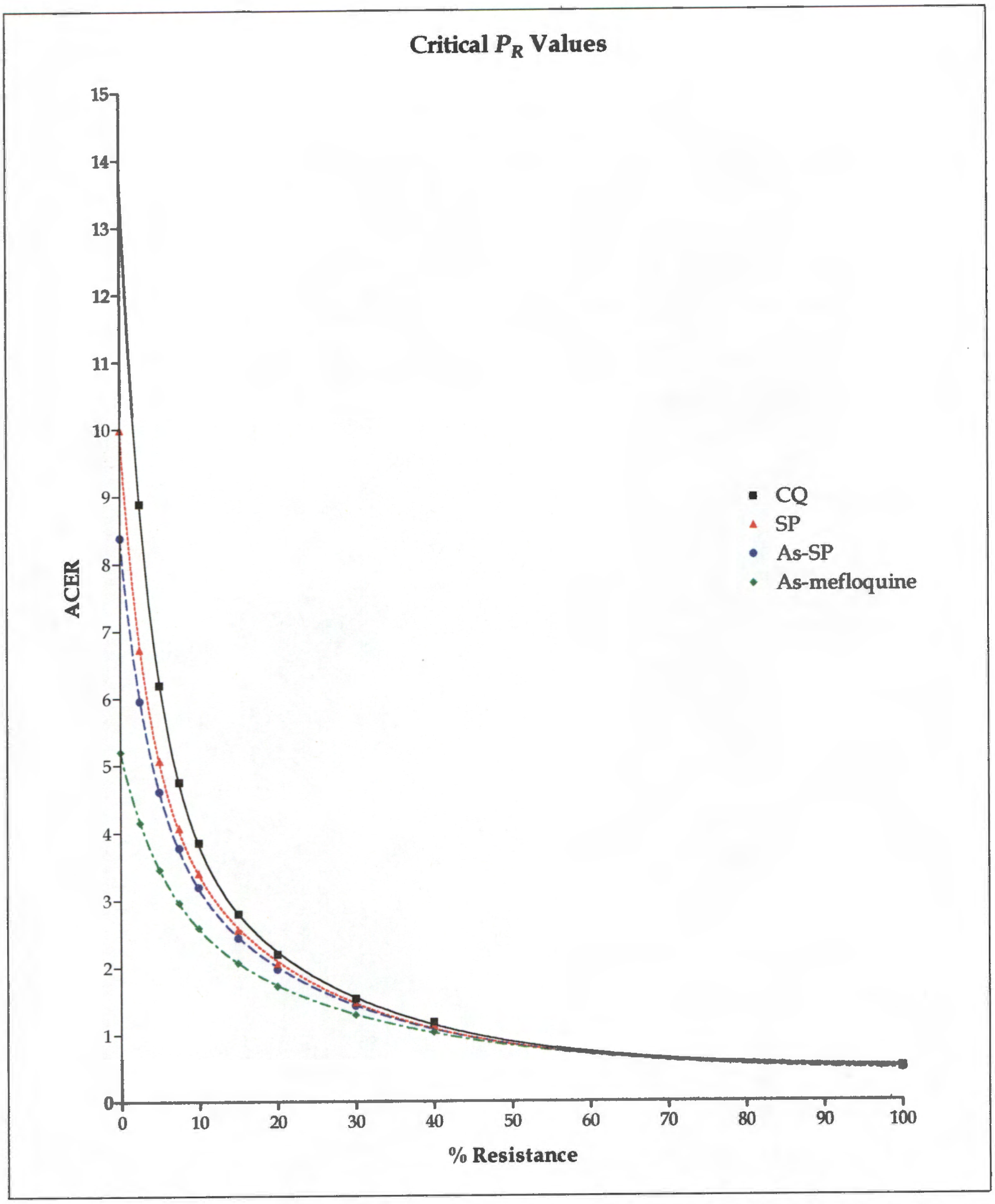

Figure 5.6. Plots illustrating the relationships between resistance and the ACER (releative to chloroquine) for sulfadoxine-pyrimethamine, artesunate-SP and artesunate-mefloquine.

5.8.5.1. Chloroquine

In order for chloroquine to be as cost-effective than sulfadoxine-pyrimethamine in the Tonga district, its *in vivo* resistance prevalence would have to be 7.30% (using the curves derived in Table 5.85); to be more cost-effective than artesunate-SP, resistance would have to be under

2.43%, and to be more cost-effective than artesunate-mefloquine, resistance would have to be lower than 5.88%.

5.8.5.2. *Sulfadoxine-pyrimethamine*

For sulfadoxine-pyrimethamine to be more cost-effective than artesunate-SP, its *in vivo* resistance level would need to be under 0.54%, and to be more cost-effective than artesunate-mefloquine, P_R would have to be lower than 4.14%.

5.8.5.3. *Artesunate Combinations*

Artesunate-SP and artesunate-mefloquine would have equal cost-effectiveness if the *in vivo* prevalence of *P. falciparum* resistance to artesunate-SP were 3.68%.

COSTS INCURRED BY PATIENTS

6.1. Introduction

In addition to the costs incurred by the State in the treatment of falciparum malaria, considerable expense may be borne by patients. Although the public health system charges only a minimal fee to patients, each patient is required to travel to the clinic or hospital from their place of residence and back again, often several times. In the rural districts of Shongwe and Tonga, where an overwhelming proportion of the population is African, it was found that 81% of respondents in the Central Statistical Service's October 1995 household study in Mpumalanga made use of public health care facilities. Of those, 45% specifically went to a hospital, 51% preferred going to a clinic, but only 4% had no preference (Orkin *et al*, 1998).

The same report revealed that health facilities were, in most cases, relatively close to households. In 25% of African households, a medical facility was within 1 km, 38% reported that one was located within 5 km of their home, and 37% were more than 5 km from a facility.

The time taken by rural African families to reach their closest primary health care facility was substantial. 25% of families were within 15 minutes' travel, while it took 36% over an hour to reach medical help.

The costs involved in travelling were thought to be significant.

6.2. Results

6.2.1. Distances

Road distances between each source community and each of the two clinics were calculated from maps of the Barberton district obtained from the Department of Land Affairs (Directorate of Surveys and Mapping, 1988).

In 1997, the mean distance between the average patient's residential community and Naas Clinic was 5.93 km, while malaria patients visiting Mangweni Clinic travelled a mean of 11.13 km to reach it.

Each patient referred to Shongwe from Naas Clinic was transported by State vehicle, a distance of about 40.5 km. The distance covered by State vehicles when transporting patients between Mangweni and Shongwe was about 37 km.

The majority of Naas Clinic's malaria patient intake was divided between Albertsnek, a small settlement a little under 5 kilometres from the Mozambique border, and Naas itself; they accounted for 28.02% (102 notifications) and 25.55% (93 notifications, 10 km distant) respectively. Naas Clinic's major patient intake seems to be divided among a relatively small number of sites; in addition to Naas and Albertsnek, only three other sites, Block C (Sibayeni, 0.5 km distant, 12.09%, 44 notifications), Block D (Ngwenyeni, 5 km distant, 9.89%, 36 notifications) and Block B (KwaSibhejane, 8 km distant, 4.40%, 16 notifications) accounted for more than 4% of patients. All three, however, are located relatively close to Naas Clinic, with number of patients increasing in proportion to decreasing distance from the clinic. This relationship is not significant, however ($r^2 = 2.977$).

The largest contributor community to Mangweni Clinic's malaria patient intake is Mangweni itself (34.70%, 152 notifications). The remaining contributors above 4% are roughly evenly divided between Mbuzini (28 km distant, 7.31%, 32 notifications); Vukuzenzele (13.5 km distant, 7.08%, 31 notifications); Figtree (11.5 km, 6.62%, 29 notifications); Block A (8 km distant, 5.94%, 26 notifications); Mandulo (11.5 km distant, 5.25%, 23 notifications); Mananga (30 km distant, 5.02%, 22 notifications); and Masibekela (15 km distant, 4.79%, 21 notifications). Again, no significant linear relationship could be shown between the distance of the clinic from feeder community and number of notifications.

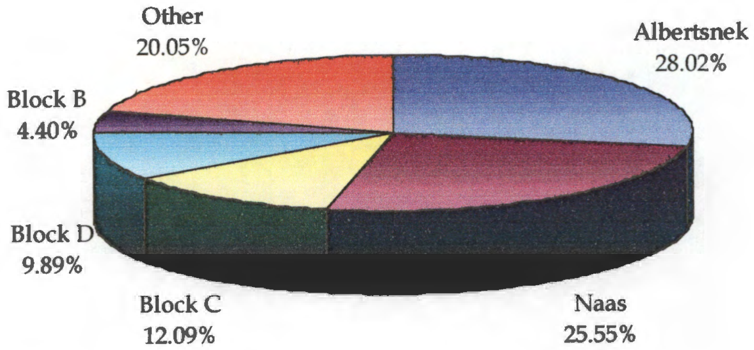

Figure 6.1. Breakdown of communities from which malaria cases notified at Naas Clinic originated. Notifications were almost evenly divided between the largest discrete group of patients (102, 28.02%), resident in Albertsnek, and the next largest (93, 25.55%), which originated in Naas.

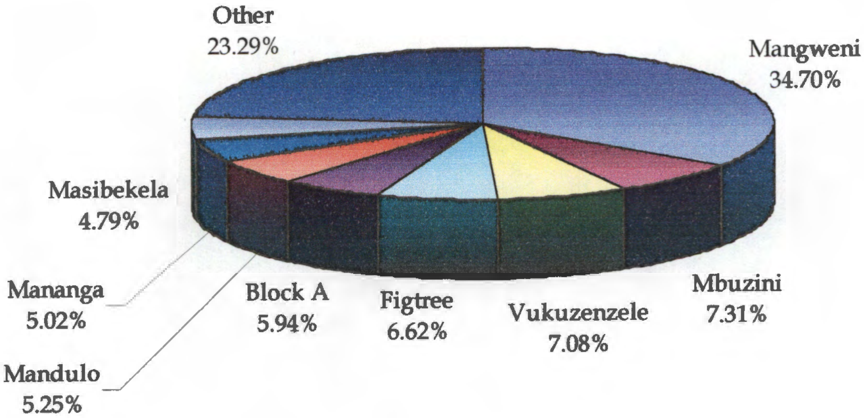

Figure 6.2. Breakdown of communities from which notifications at Mangweni Clinic originated. The largest single group of malaria patients was resident in Mangweni itself (152, 34.70%).

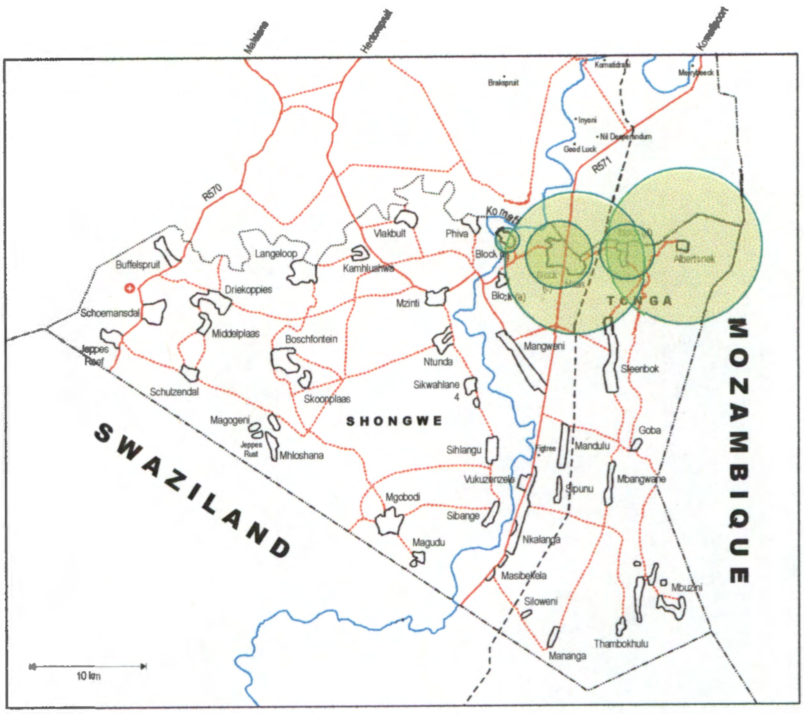

Figure 6.3. Malaria intake areas for Naas Clinic. The radii of the circles are proportionate to the number of patients originating from the settlements at the centres of the circles.

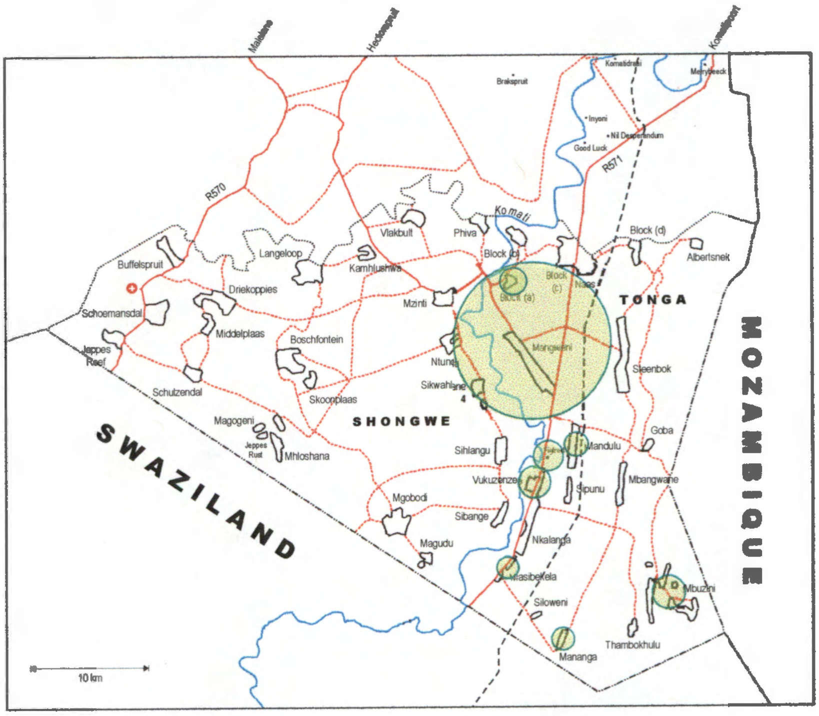

Figure 6.4. Malaria intake areas for Mangweni Clinic. The radii of the circles are proportionate to the number of patients originating from the settlements at the centres of the circles.

6.2.2. Costs Incurred by Patients

6.2.2.1. Treatment Costs

Each patient treated, with the exception of pregnant women and children under 6, was charged R6.00 per clinic visit and R10.00 per hospital admission. Patients were charged these fees regardless of disease or therapy.

Chloroquine

Using chloroquine as first-line agent, average cost per patient depends on *R*, the resistance modifier.

Clinic	No of patients	Total Clinic Charges (ZAR)	*R*	No of Referrals	Total Hospital Charges (ZAR)	Total per Clinic (ZAR)	Total per Patient (ZAR)
Naas	236	1 416.00	0.3354 ± 0.07188	79.15 ± 16.96	791.50 ± 169.60	2 207.50 ± 169.60	9.35 ± 0.72
Mangweni	271	1 626.00	0.3354 ± 0.07188	90.89 ± 19.48	908.90 ± 194.80	2 534.90 ± 194.80	9.35 ± 0.72
Mean							**9.35 ± 0.72** ***(US$ 2.03 ± US$ 0.16)***

Table 6.1. Average cost borne by a malaria patient treated with chloroquine at a clinic in 1997. US$1.00 = ZAR 4.6072.

Sulfadoxine-pyrimethamine

Substitution of chloroquine by sulfadoxine-pyrimethamine results in altered per-patient costs, since *R* is different.

Clinic	No of patients	Total Clinic Charges (ZAR)	*R*	No of Referrals	Total Hospital Charges (ZAR)	Total per Clinic (ZAR)	Total per Patient (ZAR)
Naas	236	1416.00	0.0835 ± 0.0083	9.09 ± 1.96	90.90 ± 19.60	1506.90 ± 19.60	6.38 ± 0.08
Mangweni	271	1626.00	0.0835 ± 0.0083	10.43 ± 2.25	104.30 ± 22.50	1 730.30 ± 22.50	6.38 ± 0.08
Mean							**6.38 ± 0.08** ***(US$ 1.38 ± US$ 0.02)***

Table 6.2. Average cost borne by a malaria patient treated with sulfadoxine-pyrimethamine at a clinic in 1997. US$1.00 = ZAR 4.6072.

6.2.2.2. *Travel Costs*

Each patient accepted into the 1998 *in vivo* sulfadoxine-pyrimethamine effectiveness study was interviewed to determine his or her method of travel to and from the study clinic at which they were recruited. The results appear in the table below.

Number of patients (of 77)	Method of travel	Mean Direct Cost per Patient (ZAR)
2 (2.60%)	Bicycle	0.00
3 (3.90%)	Family car	2.29*
9 (11.69%)	Hired transport	47.22
15 (19.48%)	On foot	0.00
48 (62.34%)	Taxi	5.44

Table 6.3. Travel methods among the Tonga population. * The mean distance covered by patients using a family-owned vehicle was 4.33 km, which is equivalent to a travel cost of R2.29 per trip to and from the clinic. A mean cost-per-kilometre of R0.264 per km was used, as estimated in Section 4.2.7. This figure is assumed to be reasonable due to the overall advanced age of privately owned vehicles and poor roads in the region. US$1.00 = ZAR 4.6072.

Of the 125 patients recruited for the *in vivo* study, 48 did not initially present at either of the clinics, and have therefore been excluded from this aspect of the study. Total travel cost to the remaining 77 patients recruited for the study was R692.97, or a mean travel cost of R9.00 per patient.

Patients requiring admission to hospital were assumed to be conveyed by the ambulance service described in Section 4.2.7, thus incurring no further travel costs.

6.2.2.3. *Other Costs*

Other costs are borne by patients. These include:

- The income lost as a result of time spent absent from work while visiting the clinic and, if necessary, the hospital;
- The costs of paying child-minders; and
- The indirect costs brought about by the patient's absence from home.

Due to the extremely high levels of unemployment in the subregion, lost income was thought to be less important a factor than might be expected. Also, it was noted during the course of the study that child-minders are not often utilised; children generally accompany their parents. An informal crèche exists at the hospital for this reason.

The above additional costs to patients cannot be assumed to be negligible, but the evaluation of these proved to be beyond the scope of this work.

6.2.2.4. *Summary*

Chloroquine Cost (ZAR)			**Sulfadoxine-pyrimethamine (ZAR)**		
Treatment Cost	**Travel Cost**	**Total Cost (ZAR)**	**Treatment Cost**	**Travel Cost**	**Total Cost (ZAR)**
9.35 ± 0.72	9.00	**18.35 ± 0.72** ***(US$ 3.98 ± US$ 0.16)***	6.38 ± 0.08	9.00	**15.38 ± 0.08** ***(US$ 3.34 ± US$ 0.02)***

Table 6.4. Projected costs per patient for malaria treatment in 1997. US$1.00 = ZAR 4.6072.

The introduction of sulfadoxine-pyrimethamine brought about an estimated net saving of 16.19% in treatment and travel costs borne by patients when compared with chloroquine.

6.2.3. *Costs Related to Death*

A critical aspect related to patient costs is that of the cost of death. While this is thought to affect patient-incurred costs enormously, it was not possible to quantify in this study. A detailed discussion of the relevant considerations appears as Section 1.8.5, on page 28. The mortality rate, country-wide, was 0.45% in 1997, translating to 2.3 deaths amongst the 507 patients included in costing (see Figure 1.3, page 4).

Chapter 7

DISCUSSION OF RESULTS & CONCLUSION

The following objectives were met:

- The baseline malaria situation in the Tonga district was elucidated, with respect to malaria caseload and demographic profiles.
- A model was constructed to relate the variable and fixed direct costs of malaria to the public health system. Data from all required categories were collected and analysed using the model, using sulfadoxine-pyrimethamine as a starting point. Chloroquine and a range of other drugs were modelled using their respective *in vivo* probabilities of resistance and drug costs per treatment course.
- The model was used to generate an average cost-effectiveness ratio (ACER) for every drug relative to chloroquine.

The following objectives were partially met:

- The average cost of treatment to the patient was assessed (including transport costs and direct cost of treatment), in terms of average cost per notified patient. However, the detail of results obtained was not comprehensive.

No model was constructed for chlorproguanil-dapsone ('LapDap'); insufficient data was available.

7.1. Baseline Study of Malaria in the Nkomazi Region of Mpumalanga

The rapid increase in the number of malaria cases in the Mpumalanga Lowveld during the 1987-1996 period, as seen in this analysis, is well-described (Dürrheim & Whittaker, 1996; Kruger *et al*, 1996). The Lowveld region, specifically the part thereof that includes the Shongwe and Tonga districts, where this study was based, borders on Mozambique in the east and Swaziland in the south. Mozambique's malaria control programme is hamstrung by a lack of funds for healthcare and a very weak economy. Malaria in that country is endemic and difficult to control (le Sueur *et al*, 1996).

It may be inferred that much of the labour demand in the Shongwe and Tonga districts is filled by illegal Mozambiquan immigrants who cross the border in order to find employment, bringing malaria into the district, as is the case in KwaZulu Natal (Mnzava *et al*, 1998; Ngxongo, 1993). While malaria control in South Africa is relatively effective, imported malaria is thought to partially account for the high prevalence of malaria in South Africa's border regions: it is found in the Northern Province (bordering Botswana) and northern KwaZulu-Natal (bordering southern Mozambique and Swaziland) as well (Sharp, 1996). Mpumalanga's geographical and climatic profile creates ideal breeding conditions for *Anopheles arabiensis*, the principal vector for *P. falciparum* malaria in the subcontinent. Additionally, the role of increasing chloroquine resistance in increasing transmission is likely to be significant.

Increased rainfall and higher temperatures in the region in recent years due to the El Nino effect, as well as political changes in border controls, account for the substantial increase in malaria in 1996.

During the 1991-1996 period, a mean total of 57.69% of malaria smears examined by the district laboratory originated at Shongwe Hospital, which is located a substantially greater distance from the border than all the other facilities with more than 1% of the district malaria load. This is an area otherwise free of the disease. This is largely explained by the results of an internal study conducted at Shongwe Hospital, which revealed that a lack of communication between the outlying clinics and slow laboratory results resulted in approximately 90% of thick smears being repeated upon admission to the hospital (personal communication, E Athan). This renders the validity of the Shongwe Hospital thick smear records as an epidemiological tool highly suspect.

The clinics at Naas and Mangweni carry a degree of prestige in the community, and are perceived as being more efficient than the day clinics. Patients therefore might travel further to get to these facilities, even though another clinic might be nearer.

Naas and Mangweni are open twenty-four hours every day, and therefore more accessible than other clinics in the region. It is likely that their loads would drop significantly if they opened only eight hours a day. Of the day clinics with a substantial number of malaria cases, Mbuzini is both close to the Mozambique border and a substantial distance from the hospital and the 24-hour clinics. Steenbok is also near the border. Mzinti and Sihlangu are in Shongwe, on the South African side of the Komati River, and farther from the border than any of the other high-caseload clinics. Block C has a very low malaria profile compared to its close neighbour, Naas. Naas is a 24-hour clinic and is the most frequently visited primary health care facility in the Sibayeni area. Block B is located in KwaSibhejane, which is in turn located in the crook of a bend in the Komati River. The geography of the region may play a role in the relatively high number of malaria notifications at that clinic, since breeding conditions for the *Anopheles* mosquito appear to be optimal at the site.

Naas and Mangweni Clinics were chosen as sentinel sites primarily because of their concomitant use as sentinel sites for the *in vivo* sulfadoxine-pyrimethamine study being conducted by the Medical Research Council of South Africa and the provincial malaria control programme, but also because of their relatively central locations, and the fact that they do not close.

In absolute numbers of malaria notifications, Mangweni is ranked lower than both Mbuzini and Steenbok. This bias is probably attributable to the effect of the substantially-higher number of malaria cases in 1996, concomitant with their close proximity to the Moazambiquan border.

All thick smears listed as positive for malaria in the records at the laboratory are also listed as *P. falciparum* infections. In a sample consisting of 4 406 smears found to contain trophozoites, none was found to be infected with *P. vivax*, *P. ovale* or *P. malariae*. These results do not concur with the findings of the *in vivo* study of chloroquine resistance carried out by the Mpumalanga Department of Health and Welfare and the MRC (Govere *et al*, 1998); this study detected traces of the three non-falciparum species. It would seem likely that all infections diagnosed by microscopy were routinely registered as *P. falciparum*, without species determination being done. However, since the 1997 introduction of ICT kits, which are species-specific, this can no longer happen with *P. falciparum*. However, this raises concerns regarding the detection of other malarial species, which, after testing negative for falciparum, may not be correctly diagnosed as malaria. Training of clinical staff is probably necessary, if this has not already been done.

7.1.1. *Parasite Detection Rates*

At primary health care clinic level, detection rates (number of thick smears positive for malaria versus number of thick smears examined) were 2.35% ± 0.44%, or about 1 positive case in every 43 smears examined. The positivity rate at Shongwe Hospital was markedly higher (9.29% ± 2.04%). The difference may be due to greater severity of malaria symptoms appearing at the hospital as opposed to the clinics, where headaches and fever are automatically assumed to be possible cases of malaria and tested. Differences in staff expertise may also play a role. The routine re-testing of patients referred with malaria from rural clinics is a clear source of bias.

A seasonal fluctuation in thick smear positivity rate was detected (Fig. 3.4, p 48), with peaks corresponding to high positivity occurring approximately annually, in the high transmission periods of the malaria season between January and March. This was an expected result, as the rains began and temperatures began to rise.

Thick smears originating from Shongwe accounted for 23.4% of those analysed. The clinics at Mbuzini, Steenbok, Naas, Mangweni, and Block B also accounted for large numbers of tests analysed at the laboratory, which was not unexpected, considering the high number of malaria cases presenting at those sites and the resulting selection bias of staff.

Thick smears have not been used for the detection of malaria since the full-scale introduction of immunochromatographic tests (ICTs) for *P. falciparum* in the district in 1997.

7.1.2. *The Active Surveillance Programme*

The diagnostic efficiency of the active surveillance programme in the region is far lower. Of 404 836 thick smears evaluated, only 1 639 cases of malaria were detected, representing an overall positivity rate of 0.399% ± 0.047%, or 1 in 250. During the six-year period under investigation, the annual hit rate varied between 1 in 103 (1991) and 1 in 513 (1993). In contrast, passive surveillance at clinic and hospital level detected 4 406 malaria cases (2.7 times more) using 89 939 thick smears, almost fivefold fewer tests. Bearing in mind the reportedly high costs of running the programme, the results suggest that passive surveillance alone is more cost-effective. However, active surveillance may have an effect on treatment-seeking behaviour. Visits from active surveillance personnel may increase community awareness of malaria and thereby encourage future malaria patients to seek treatment from public health care centres rather than from traditional healers. Active surveillance may also increase early treatment of malaria, thus reducing transmission. This suggests an area for additional pharmacoeconomic research; an appraisal of the costs and benefits of the active surveillance programme.

The on-the-spot treatment of suspected malaria cases with antimalarials no longer represents as large a resistance-inducing risk as it once did. The advent of ICTs allows the immediate and accurate diagnosis of falciparum malaria, something not possible before. Drugs would therefore only be administered when appropriate.

7.1.3. *General Observations*

The trend towards seasonal peaks in thick smear positivity noted in passive detection at the clinics and Shongwe Hospital was absent in the positivity rates associated with the active surveillance programme, with the exception of an increase in 1996 (Fig 3.5, page 51). Positivity never reached 3% between 1991 and 1996, and decreased to half its 1991 levels in mid-1992, where it remained until the 1996 epidemic. Cases were passively detected outside the malaria season in greater numbers than during the season. A possible explanation is the detection of low-grade infections in semi-immune individuals originating in holoendemic transmission areas, such as Mozambique. It is also likely that non-immune persons contracting falciparum malaria would seek medical attention almost immediately, leading to their detection at a clinic or hospital rather than at the active surveillance level, which would account for the lower or equivalent numbers observed during peak season. It is not apparent why the same semi-immune carriers would not be detected at an equal rate during peak season; one possibility is seasonal demand for labour. Harvesting on the farms in the region, for example, might require hiring extra staff, generally recruited from the immigrant labour pool.

The malaria caseloads at Naas (236 notifications, 0.78% of total patient throughput) and Mangweni (271 notifications, 1.10% of total patient throughput) are lower than those seen at the day clinics with the highest throughput of malaria patients, but the smaller day-clinics lack the infrastructure to support studies of this size. Additionally, the numbers of patients seen by the smaller clinics at Mbuzini (548 notifications, 5.79%) and Steenbok (175 notifications, 2.29%) are comparable to the 24-hour clinics.

The demographic data show that mean age of malaria patients in the Nkomazi district, comprising today's Shongwe and Tonga districts, was far lower than that found in other districts such as Barberton, White River, and Nelspruit. This may be due to a younger general population in the region compared to the others. It may also reveal that mean age of malaria patients in the area is increasing with time, although most cases still occur in the prepubescent population.

The mean age of new malaria patients throughout the region is relatively low in comparison to the general population, but this is explained by the pyramid structure of the South African population as a whole. The area comprises a 'young population' typical of many developing countries. According to 1995 census estimates, 39% of the African population of Mpumalanga is under 15 years, and only 3% is over 65 (Orkin *et al*, 1998). Only the African population in the area has been highlighted, since it is this group which makes virtually exclusive use of the public clinics and Shongwe Hospital. Privileged populations rely on private sector providers.

7.2. Modelling

7.2.1. *Development of the Model*

The model was successfully constructed to detail carefully defined, discrete variable and fixed costs accrued by the public health system as a result of malaria, based on the 1997 *in vivo* study of sulfadoxine-pyrimethamine efficacy in the Tonga district of Mpumalanga.

However, the model has a number of inherent shortcomings. It assumes that all patients suffering from malaria eventually present at a primary health care facility, as South Africans comprise a non-immune population who will become symptomatic when infected. They must therefore receive adequate treatment or die. Some patients may seek treatment from traditional healers, but it seems unlikely that such treatment will be effective; in most, traditional treatment is likely to fail and other sources of treatment will need to be sought. Since formal private practitioners are both scarce and expensive, it is reasonable to assume that a public health facility -- such as a rural clinic -- will be visited by the majority of patients at some point during the course of their infections.

For those patients not cured by the first-line antimalarial, a return rate of 70% ± 15% was estimated, based upon expert interviews with three public health care workers and officials in the region. Owing to small discrepancies in their opinions, a sensitivity adjustment was included. No data regarding treatment-seeking behaviour among rural Mpumalanga populations exists. However, since cases were estimated to have a 95% probability of falling between 55% and 85%, this was considered a reasonable method of assessing return rate, especially since there is no other effective source of treatment in the area. The model indirectly allows for patients returning to other clinics for treatment, as costs between 24-hour and day clinics did not differ significantly. Staff numbers were identical (personal communication, R Raubenheimer, Mpumalanga Department of Health and Welfare) and other parameters were either identical or the difference was insignificant (fixed costs did not vary significantly from clinic to clinic, regardless of whether they were open 8 hours or 24 hours a day).

The model did not take into account expenses associated with the pharmacodynamics of the drugs themselves. Sulfadoxine-pyrimethamine, for instance, does not necessarily alleviate symptoms, but merely clears parasitemia. Patients in whom the drug has been effective may nonetheless return to the clinic on the assumption that the drug has not worked.

Side effects of the drugs were also not considered. While the side effect profiles of chloroquine are mild and unlikely to cause problems in first line treatment, other agents may generate more serious adverse effects. The neuropsychiatric effects associated with mefloquine are usually mild at therapeutic doses, but severe derangement is known to occur in an estimated 1 in 215 cases treated therapeutically. Sulfadoxine-pyrimethamine therapy is associated with significant, although rare, side effects, notably severe cutaneous adverse reactions (SCARs), including erythema exudativum multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and cutaneous vasculitis. Frequency appears to vary according to geographical location. The US Centers for Disease Control reported cutaneous reactions in 1:5000 to 1:8000 cases, with fatalities in the order of 1:10000 to 1:25000 (Tester-Dalderup, 1996). Other side effects of SP include hematological and respiratory adverse effects. No severe adverse events have been reported since the introduction of SP as first-line therapy for malaria in Mpumalanga. Halofantrine treatment carries with it the risk of severe cardiac adverse events, especially where a pre-existing cardiac conduction abnormality exists. The drug also exhibits a severe interaction profile with chloroquine, quinine and possibly mefloquine (Tester-Dalderup, 1996). Amodiaquine carries a risk of agranulocytosis.

Artesunate's side effect profile remains unclear. There appears to be no serious side effect thus far, but its long term effects are unknown; its neurological effects on laboratory animals are a source of concern. Pyronaridine appears to be safe, but substantial research followed by careful post-marketing surveillance must be conducted before confidence may be attached to this, considering its structural homology to amodiaquine.

The impact of side effects on costs may be considerable. For instance, a cardiac adverse event (in the case of halofantrine) would likely result in an extended hospital stay. Hospitalisation is the most costly element in the costs associated with first line antimalarial treatment. If a significant number of these adverse effects were to manifest, it would dramatically reduce the cost-effectiveness of halofantrine.

The model succeeds mainly in determining the relative cost-effectiveness of the antimalarials examined, rather than providing an exact quantitative assessment of cost. Although not every cost was measured, every drug was assumed to be used within the same public health infrastructure; none were assumed to require any substantial restructuring of the way in which first line malaria cases are treated. Further, drug resistance levels and costs were as accurate as possible. Therefore, the relative positions of the drugs and combinations on the ranking scale in Figure 5.2 are likely to remain accurate.

Time was a factor that was excluded by the design of the model, which concentrated on a single year, 1997, and modelled the predicted relative costs of using each of the 11 drugs and combinations evaluated in the study for first line therapy during that single year.

Many things change from year to year: malaria transmission, drug costs (including the expiry of patents), and particularly *in vivo* drug resistance, which is accelerated as parasite populations are exposed to antimalarial agents. The rate of developing resistance was not taken into account, but is of critical importance when deciding whether to change first line treatment, and if so, which drug or combination to adopt. For instance, the experience so far suggests that the selection of specific mutations bestowing sulfadoxine-pyrimethamine resistance on *P. falciparum* is a great deal faster than selection for artesunate resistance.

Drug costs, especially, are a source of variation, but their impact on the ACER is relatively small. However, a reduction in the costs of both quinine and sulfadoxine-pyrimethamine, as described in Kenya, is enough to change the ACER rankings. SP, using these costs and assuming equal *in vivo* resistance, would become more cost-effective than artesunate-mefloquine. However, the Kenyan cost of mefloquine is not known and would likely change the order, and resistance to SP in Kenya is higher than in South Africa. This underscores the importance of resistance as a determinant of cost-effectiveness, rather than drug cost.

7.2.2. *Modelling of the Drugs*

Chloroquine and sulfadoxine-pyrimethamine were modelled most accurately. Exact data on cost and *in vivo* resistance by *P. falciparum* to both drugs in the Tonga district were known.

In vivo drug resistance is the single most important factor determining cost-effectiveness. It has been shown that large variations in drug cost do not affect the ACER significantly. The only exception is quinine, the second line drug, and then only if resistance is high. In the case of high resistance, variations in the price of quinine will affect the ACER, since the drug is used to treat hospitalised patients, numbers of which increase in proportion to resistance. All other factors, such as staff time and consumables, are governed by resistance alone.

P_R for amodiaquine was thought to be accurate, owing to the fact that it was based upon a review of 15 clinical trials, most within sub-Saharan Africa. P_Rs for co-artemether, atovaquone-proguanil, and halofantrine were based upon careful selection of single studies within sub-Saharan Africa, but these estimates of the proportion of resistant cases may not be applicable to South Africa. The model relies on the assumption that they are accurate.

Mefloquine resistance developed extremely quickly in Southeast Asia within 5 years of its introduction (White, 1992). Recent *in vitro* studies of *P. falciparum* isolates from the Mpumalanga region suggest that resistance has not yet developed (Freese *et al*, 1994). The use of mefloquine in South Africa as a prophylactic agent would, however, suggest that some drug pressure has already taken place and that development of resistance is more likely.

Costs could not accurately be obtained in the case of either amodiaquine or co-artemether, considering the drugs are not registered in South Africa and an estimated price had to be estimated based upon export prices in US dollars and Swiss francs, respectively. Multinational drug companies tend to standardise prices globally.

One million doses per annum of atovaquone-proguanil, in the form of Malarone, have been donated to African malaria control programmes by Glaxo Wellcome. Free supplies of the drug becoming available in South Africa were not considered during the development of the model, since this is unlikely to occur.

Artesunate (and its combinations) and pyronaridine presented problems with respect to both drug prices and estimates of *in vivo* resistance. As mentioned earlier, South Africa is perceived by multinational drug companies as more able to pay high prices for drugs than other African nations. Artesunate was valued according to its Thai market price, which was later confirmed as being the most realistic estimate of what it might cost in Africa (personal communication, M Gomes, Artesunate Product Manager, Special Programme for Research and Training in Tropical Diseases, WHO). The South African price may well be higher, though, and this should be taken into account when comparing artesunate and its combinations to drugs such as atovaquone-proguanil, which are registered in South Africa. The projected price of pyronaridine is estimated to be $3.00 per adult course in 1996 (Winstanley, 1996) but it is unclear whether this will apply to South Africa.

The artemisinin derivatives have been slow to induce resistance, even in the Southeast Asian milieu of high drug pressure. For that reason, it was reasonable to assume that resistance in southern Africa, where the drug has never been used, is nil. Pyronaridine resistance has already appeared in Southeast Asia (Looareesuwan *et al*, 1996), but has not yet been reported in Africa.

Some of the data used to model some of the drugs were not ideal, and for this reason it is necessary to 'grade' each drug or combination according to the estimated accuracy of the results. The most accurately modelled drugs were sulfadoxine-pyrimethamine and chloroquine, followed by amodiaquine, halofantrine, atovaquone-proguanil, co-artemether, artesunate and its combinations, and finally pyronaridine.

7.2.3. *Recommendations*

On the basis of the model, it is clear that artesunate and its combinations, as well as pyronaridine, potentially represent the most cost-effective treatment options in the region. Although artesunate is first-rank, in practice and allowing for poor compliance, artesunate alone has too long a therapy regimen to be a serious alternative for first-line treatment. Its deployment as a monotherapeutic option may also be unwise from the standpoint of developing drug resistance. Following from this, artesunate in combination with mefloquine or sulfadoxine-pyrimethamine is recommended as replacement therapy before the level of SP resistance becomes too high. There are several reasons for this:

- Primarily, the superior cost-effectiveness of artesunate-SP and artesunate-mefloquine compared with other agents and combinations;
- The advantages of combination therapy in delaying the emergence of resistance (especially to SP); and
- The slow emergence of artesunate resistance in spite of high drug pressure, based upon the Southeast Asian experience.

Care should be exercised in deciding between artesunate-mefloquine and artesunate-SP. While artesunate-SP is more cost-effective than artesunate-mefloquine, SP will already have been used extensively as first line therapy in the region. If SP resistance is high, its protective function will be lessened.

A caveat in the choice of an artesunate combination for first line management of malaria is the safety of the drug. The artemisinin derivatives have been shown to be neurotoxic in high doses in laboratory animals. Artesunate is water-soluble and therefore assumed to be the least toxic of the artemisinin derivatives, and initial clinical evidence from Southeast Asia suggests that the drug is safe in therapeutic doses. However, no studies have been conducted on the neurological effects of multiple doses of artesunate on paediatric patients with developing nervous systems. Research is urgently needed in this area. Price *et al*, however, reported in April 1999 that no neurological effects were detected in 836 patients treated with artemisinin derivatives, and concluded that artemether and artesunate were safe and well-tolerated in their study population. In the same study 2 826 patients were treated with mefloquine in combination with an artemisinin derivative; this population showed a significant increase in side effects over the group treated with artemisinin derivatives alone. A third group of 1 303 patients was treated with mefloquine alone.

Some antimalarials examined here present problems not explicit in the model. Safety, efficacy, and compliance, as well as cost-effectiveness, should be considered when selecting treatment.

The fast emergence of multiple drug resistance in *P. falciparum* indicates that combination therapy represents a better long-term solution. A novel agent with high efficacy may be protected from developing resistance by combining it with another agent, thereby reducing the likelihood that any organisms will survive treatment to produce resistant populations. This is particularly true when drugs with different modes of action are combined. Also, combinations tend to use shorter treatment course regimens, which is likely to improve compliance.

The results show that it became cost-effective to switch to sulfadoxine-pyrimethamine from chloroquine when *in vivo* parasite resistance to the latter drug reached 7.30%. Based on this, it would have been cost-effective to switch to artesunate-SP when resistance to SP alone reached 0.49% in the field. These figures, however, are highly sensitive to any change in any parameter in the equation and should be interpreted as such.

7.3. Treatment Costs Incurred by Patients

The completion of the questionnaires proved problematic. An ideal approach would have been to recruit workers from the community, train them, and station them at each of the two clinics for the duration of the study. However, this was not possible due to local political considerations.

An acceptable compromise was reached by an agreement with the Mpumalanga Malaria Control Programme that their clinic assistants would collect the necessary data from the patients used in their own study.

It would have been useful to collect information regarding prior visits to traditional medical practitioners, as well as exact salary details, but this was not possible. Members of the community were extremely reluctant to divulge information of this kind. Clinical staff in the formal medical sector are perceived to frown upon traditional medicine. Patients were suspicious of questions regarding employment; many were Mozambiquan immigrants fearful of deportation, or afraid that they would be dismissed if word of their illness reached their employers (personal communications, E Athan). Patients were also extremely reluctant to divulge details of citizenship.

7.4. General Application of These Findings

African drug policy is a source of growing worldwide concern, and pharmacoeconomic evaluation is emerging as a valuable tool to assist in the formulation of rational policy. Other work in this field has already begun, such as a study on the cost-effectiveness of sub-Saharan malaria control, recently published by Goodman *et al.*

The model may be applied to malaria areas anywhere in the world where drug policy, supply and distribution is well regulated, with some modifications: area-specific factors such as local treatment-seeking behaviour and the immune status of the feeder population (semi-immune patients need not be hospitalised). Treatment policies are likely to vary from place to place, and this must be taken into account. South Africa is a special case in that treatment is supplied by the public sector.

In areas different from the Tonga district of Mpumalanga, precise details of treatment-seeking behaviour must be known in order to predict what proportion of patients are seeking treatment at clinics, what proportion are self-medicating with legal or black-market drugs, what proportion of patients are likely to return to clinics if initial treatment is a failure, and what percentage of treatment failures are hospitalised. It is critical to know what the proportions of intravenous compared with oral quinine are, at hospital level. Once these structural adaptations have been applied, the model should be generalisable.

The model may be employed to determine average cost-effectiveness ratios for interventions used in the treatment of other diseases, such as tuberculosis and sexually-transmitted diseases. Any infectious disease that is treatable using the tiered pharmacotherapy paradigm used in rural malaria management may hypothetically be modelled using the methodology developed here.

7.5. Limitations

Most notably, this study does not address the problems and costs associated with side effects of antimalarials considered in the meta-analysis, which may be substantial (as detailed in section 7.2.2). Also, additional costs incurred due to wastage of drugs and materials (such as IV drips that need to be re-sited) have not been evaluated.

This work has concentrated on direct costs, including fixed and variable costs, without considering indirect costs. Indirect costs incurred as a result of the choice of first-line antimalarial agent may be substantial.

The Tonga district is dominated by the farming industry. If a first-line antimalarial agent is ineffective in such an area of high transmission, it follows that patients will need to spend more time absent from work, either recuperating or while seeking treatment. Employees will therefore not be productive to industry while they are absent, with a resulting drop in production, which may, if the numbers of stricken employees are sufficient, have an adverse effect on the provincial economy. The high level of unemployment in the region, the proclivity of malaria for individuals under working age, and high numbers of migrant workers may also have an effect on factors such as these.

Another limitation of the study is its lack of consideration of the passage of time. The meta-analysis and model were developed with only one year, 1997, in mind.

The probability of resistance may change rapidly over time, depending on both the characteristics of the drug and the degree of drug pressure. Rates of change of drug resistance were beyond the scope of this work, but they are a major factor. Every drug and drug combination has a different rate of resistance development associated with it. Costs will appreciate with time in proportion to the inflation rate. However, if cost increases are uniform, ACERs will be largely unaffected; increasing resistance, however, will cause a significant and immediate drop in cost-effectiveness. Compliance with each drug regimen may also vary, affecting rate of change of resistance development.

A major problem with taking the perspective of the public healthcare provider is dealing with the patients who do not return to the clinics for treatment once first-line therapy fails. The estimate of a 70% ± 15% return rate is not based upon hard data and should be improved before any further studies of this kind are done. The number of 'fall-out' patients is directly related to the efficacy of the drug: patients not cured who seek help elsewhere may not achieve parasite clearance, which will likely result in an increase in transmission and therefore an increase in cases. Also, a highly inefficient public health service using an ineffective but inexpensive drug may find it is cost-effective to continue to use it unless fall-out patients are addressed.

A critical issue in ranking is compliance. No weighting was applied to any of the evaluated drug regimens to address this: artesunate, for instance, is recommended for use with a 7-day regimen. Without constant monitoring of patients, this is unlikely to be completed as directed. Sulfadoxine-pyrimethamine, conversely, is used as a single and immediate dose, making it the ideal treatment from a compliance point of view. Ranking of drugs in the model is unlikely to be seriously affected, however: apart from artesunate, only halofantrine, with its complex dosage schedule, and sulfadoxine-pyrimethamine would be affected. All the other drugs and combinations evaluated has reasonably short regimens, typically 3 days. Additionally, halofantrine's toxicity issues would effectively disqualify it as a first-line agent in any event. Sulfadoxine-pyrimethamine would likely become somewhat more cost-effective. There is a need to include compliance in future modelling of antimalarial cost-effectiveness. Without a full-scale compliance study being first conducted in Mpumalanga, any such refinement of the model would, however, be arbitrary

Finally, the study should be interpreted as a qualitative (rather than quantitative) assessment of the relative cost-effectiveness of first-line antimalarials. Not all costs were exhaustively considered, but since all the drugs were assumed to operate within the same infrastructure, ACERs would retain the same positions relative to each other. Many estimations had to be made in the assessment of costs, so a degree of error is inevitable. The sensitivity analysis will have eliminated much of this error, but the omission of certain costs cannot be corrected for, although it is identical in all the modelled drugs and therefore will not alter their relative ACERs.

7.6. Future Research

Scope exists to continue and improve on this work.

- The costs and benefits of the active surveillance programme must be determined with a view to assessing accurately its cost-effectiveness.
- Treatment-seeking behaviour in Mpumalanga patients needs to be elucidated. The proportion of patients visiting traditional healers in preference to or in combination with formal public health facilities is unknown. This is true of many areas in sub-Saharan Africa. Also, the clinic return rate of patients in whom first-line therapy fails must be accurately determined.
- The model created here may be used to assess the relative cost-effectiveness of antimalarial drugs in other parts of the country, and indeed sub-Saharan Africa and globally, with modifications for region-specific aspects.
- The indirect costs of malaria treatment should be described. Malaria is a burden not only on the public health system, but for individual patients, their caregivers, their dependants, their employers, and the nation's economic output. This information must be known for rational malaria policy to be implemented.
- The effect of compliance on cost-effectiveness must be determined.
- The effect of the use of antimalarial combinations in delaying the emergence of resistance requires further research. It is of critical importance in determining costs.

7.7. Conclusion

Falciparum malaria is concentrated in the regions of Mpumalanga close to the Mozambiquan border. The highest number of cases detected at clinic level occur at the 24-hour clinics at Mangweni and Naas, confirming their choice as sentinel sites, as well as at the day clinics at Steenbok, Mbuzini, and Block B.

The positivity rate for the clinics and the hospital is low, generally under 30%. However, this is tenfold higher than the maximum positivity recorded for the active surveillance programme in the region. The active surveillance programme detects extremely low numbers of true malaria cases in comparison to the number of tests performed, suggesting that it may be inefficient in terms of resource use.

A model for assessing the relative cost-effectiveness of various antimalarial drugs and combinations in an area of high compliance with policy and strict control of drugs was successfully developed.

The variable and fixed costs of chloroquine and sulfadoxine-pyrimethamine, when used as first line therapy for malaria, were evaluated with a view to determining cost-effectiveness. Sulfadoxine-pyrimethamine emerged as 4.8 times more cost-effective than chloroquine, confirming that its adoption as a replacement for chloroquine has been a sound decision.

Other treatment regimens were evaluated: in comparison to chloroquine, artesunate monotherapy was 13 times more cost-effective, artesunate in combination with sulfadoxine-pyrimethamine was 9.2 times more cost-effective, artesunate in combination with mefloquine was 5.6 times more cost-effective, and pyronaridine was 11.2 times more cost-effective. All represent cost-effective substitutes for the current first-line drug, sulfadoxine-pyrimethamine.

Other drugs evaluated, but found unlikely to be cost-effective in comparison to chloroquine, included amodiaquine (1.3 times as cost-effective), atovaquone-proguanil (1.7 times as cost-effective), co-artemether (1.7 times as cost-effective), halofantrine (2.1 times as cost-effective) and mefloquine (4.3 times as cost-effective). Chloroquine was the least cost-effective drug studied, despite its low cost, as a result of high resistance.

It was concluded that an artesunate combination with either sulfadoxine-pyrimethamine or mefloquine would be the most desirable successor therapy to sulfadoxine-pyrimethamine, due to the high cost-effectiveness of these, the advantages of combinations, and the slow development of artesunate resistance in other parts of the world. It is assumed that artesunate will prove to be safe.

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Appendix A: Staff Salary Tables

Position Category	**Number of staff (Q_i)**	**Time spent on malaria in months (T_i)**	**Monthly wage or salary (ZAR) (W_i)**	**Annual fringe benefits (ZAR) (FB_i)**	**Total annual cost of position including benefits (ZAR)** **$((Q_i \times [(T_i \times W_i) + FB_i]))$**
Admin					
Admin. Officer	2	12	4620.75	22179.60	155257.20
Director: Admin, Asst	1	12	7035.25	33769.20	118192.20
Data Typist Gr I	3	12	2138.25	10263.60	107767.80
Typist Gr I	2	12	2138.25	10263.60	71845.20
Admin Clerk Gr I	27	12	2138.25	10263.60	969910.20
Personnel Officer Gr I	1	12	2138.25	10263.60	35922.60
Personnel Officer Pr	1	12	4620.75	22179.60	77628.60
Account Clerk Gr I	4	12	2138.75	10263.60	143690.40
Prov Admin Clerk Gr I	5	12	2138.75	10263.60	179613.00
General and Domestic					
Cleaner I	113	12	1583.50	7600.80	3006116.40
Messenger	1	12	1583.50	7600.80	26602.80
Groundsman	20	12	1583.50	7600.80	532056.00
Porter	7	12	1583.50	7600.80	186219.60
Principal Porter	3	12	2138.25	10263.60	107767.80
Genl Worker I (Stores)	2	12	1583.50	7600.80	53205.60
Genl Worker I (Therapy)	9	12	1583.50	7600.80	239425.20
Laundry Manager	1	12	2138.25	10263.60	35922.60
Seamstress I	2	12	1583.50	7600.80	53205.60
Food Services Aid I	27	12	1583.50	7600.80	718275.60
Food Services Supervisor	5	12	2138.25	10263.60	179613.00
Laundry Aid I	27	12	1583.50	7600.80	718275.60
Laundry Aid II	1	12	1824.00	8755.20	30643.20
Laundry Manager	1	12	2138.25	10263.60	35922.60
Security Guard Gr I	1	12	1583.50	7600.80	26602.80
Operator	4	12	1583.50	7600.80	106411.20
Telecom Operator Gr I	6	12	2138.25	10263.60	215535.60
Medical					
Medical Officer	18	12	7035.25	86111.46	3069620.28
Med/Dent Super, Sen	1	12	12566.50	153813.96	304611.96

Appendix A: Staff Salary Tables

Nursing					
Nurse, Prof.	85	12	3709.50	17805.60	5297166.00
Nurse, Prof, Sen	1	12	4620.75	22179.60	77628.60
Nurs Serv, Asst Dir	2	12	7035.25	33769.20	236384.40
Staff Nurse	51	12	2533.00	12158.40	2170274.40
Staff Nurse, Sen	8	12	2996.50	14383.20	402729.60
Nursing Assistant	131	12	2138.25	10263.60	4705860.60
Supplementary Health Services					
Dietician	1	12	3709.50	17805.60	62319.60
Occ Therapist	1	12	3709.50	17805.60	62319.60
Physiotherapist	1	12	3709.50	17805.60	62319.60
Radiographer	1	12	3709.50	17805.60	62319.60
Pharmacist	2	12	3709.50	17805.60	124639.20
Emerg Care Pract	8	12	2533.00	12158.40	340435.20
Food Services Manager	2	12	2138.25	10263.60	71845.20
Operator	3	12	1583.50	7600.80	79808.40
SASO: Therapy Asst	2	12	1583.50	7600.80	53205.60
Aux Services Officer I	13	12	1583.50	7600.80	345836.40
Primary Health Care					
Med/Dent Superintendent	1	12	10391.00	127185.84	251877.84
Nurse, Prof	3	12	3709.50	17805.60	186958.80
Nurs Serv, Asst Dir	2	12	7035.25	33769.20	236384.40
Admin Clerk Gr I	2	12	2138.25	10263.60	71845.20
Maintenance					
Tradesman Aid I	12	12	1583.50	7600.80	319233.60
Genl Worker I (Incin)	4	12	1583.50	7600.80	106411.20
Operator	5	12	1583.50	7600.80	133014.00
Lab Services					
Medical Technologist	8	12	3709.50	17805.60	498556.80
Total				**R**	**27 465 234.48**

Table A.1. Breakdown of staff makeup and salaries at Shongwe Hospital in 1997.

Appendix A: Staff Salary Tables

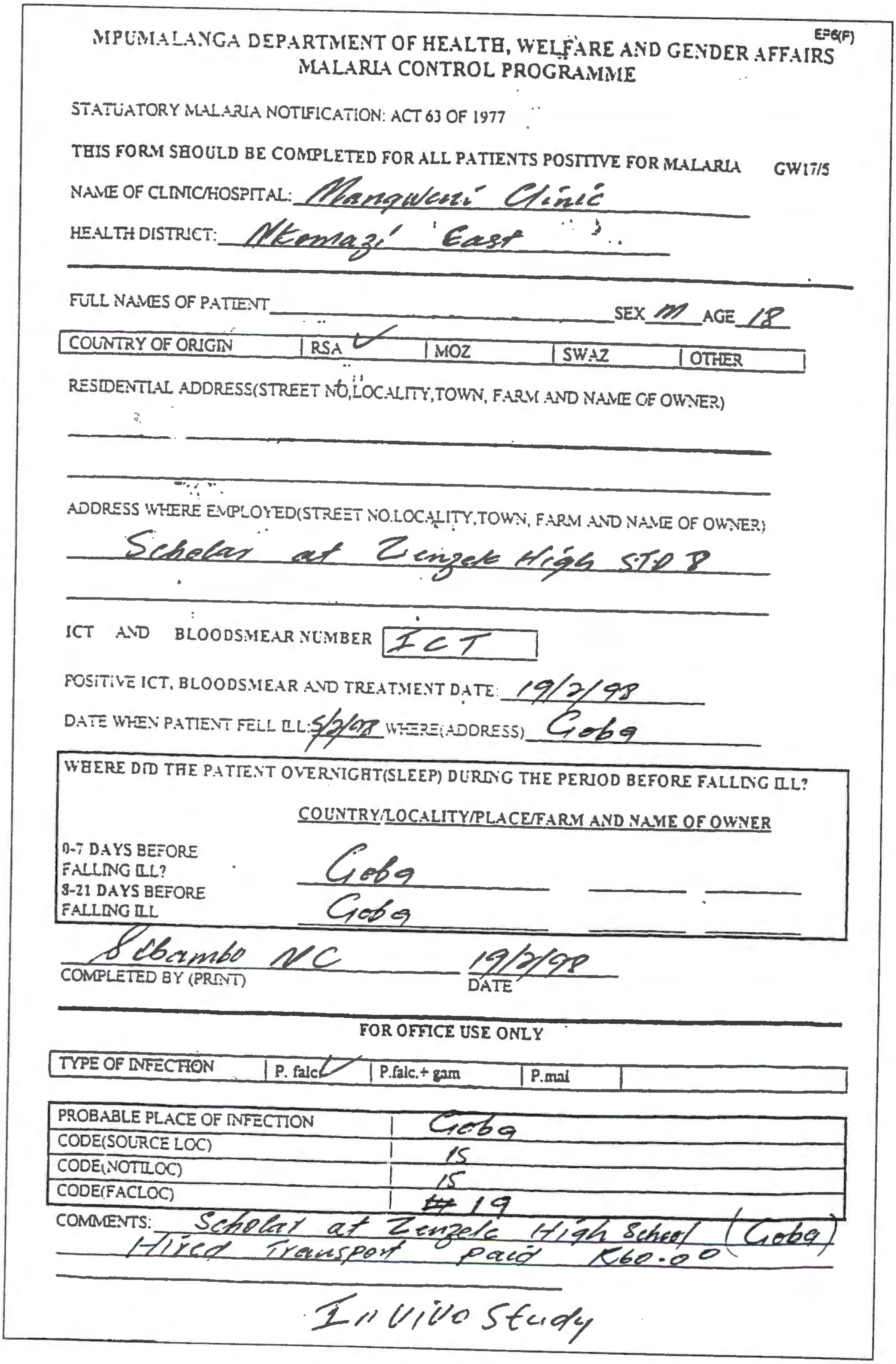
Post	Number	Annual Salary	Additional Benefits	Total Annual Salary for Post Including Benefits
Prof. nurse	11	44514.00	40%	685515.60
Staff nurse	1	30396.00	40%	42554.40
Emerg. care practitioner	3	30396.00	40%	127663.20
Admin. clerk	1	25659.00	40%	35922.60
Cleaner	5	19002.00	40%	133014.00
Groundsman	1	19002.00	40%	26602.80
Nursing assts	7	25659.00	40%	251458.20
Total			**R**	**1 302 730.80**

Table A.2. Breakdown of staff makeup and salaries at Naas Clinic in 1997.

Post	Number	Annual Salary	Additional Benefits	Total Annual Salary for Post Including Benefits
Prof. nurse	11	44514.00	40%	685515.60
Staff nurse	1	30396.00	40%	42554.40
Emerg. care practitioner	4	30396.00	40%	170217.60
Admin. clerk	1	25659.00	40%	35922.60
Cleaner	5	19002.00	40%	133014.00
Groundsman	1	19002.00	40%	26602.80
Nursing assts	7	25659.00	40%	251458.20
Total			**R**	**1 345 285.20**

Table A.3. Breakdown of staff makeup and salaries at Mangweni Clinic in 1997.

Appendix B: Sample in vivo study questionnaire (Mpumalanga Malaria Control Programme). The name and address fields have been erased to preserve patient anonymity.



EP6(F)

MPUMALANGA DEPARTMENT OF HEALTH, WELFARE AND GENDER AFFAIRS
MALARIA CONTROL PROGRAMME

STATUATORY MALARIA NOTIFICATION: ACT 63 OF 1977

THIS FORM SHOULD BE COMPLETED FOR ALL PATIENTS POSITIVE FOR MALARIA GW17/5

NAME OF CLINIC/HOSPITAL: Mangweni Clinic

HEALTH DISTRICT: Nkomazi East

FULL NAMES OF PATIENT ______ SEX M AGE 18

COUNTRY OF ORIGIN	RSA ✓	MOZ	SWAZ	OTHER

RESIDENTIAL ADDRESS(STREET NO,LOCALITY,TOWN, FARM AND NAME OF OWNER)

ADDRESS WHERE EMPLOYED(STREET NO.LOCALITY,TOWN, FARM AND NAME OF OWNER)

Scholar at Zenzele High STD 8

ICT AND BLOODSMEAR NUMBER ICT

POSITIVE ICT, BLOODSMEAR AND TREATMENT DATE: 19/2/98

DATE WHEN PATIENT FELL ILL: 5/2/98 WHERE(ADDRESS) Goba

WHERE DID THE PATIENT OVERNIGHT(SLEEP) DURING THE PERIOD BEFORE FALLING ILL?

	COUNTRY/LOCALITY/PLACE/FARM AND NAME OF OWNER		
0-7 DAYS BEFORE FALLING ILL?	Goba		
8-21 DAYS BEFORE FALLING ILL	Goba		

S Ubambo NC
COMPLETED BY (PRINT)

19/2/98
DATE

FOR OFFICE USE ONLY

TYPE OF INFECTION	P. falc ✓	P.falc.+ gam	P.mal	

PROBABLE PLACE OF INFECTION	Goba
CODE(SOURCE LOC)	15
CODE(NOTILOC)	15
CODE(FACLOC)	~~14~~ 19

COMMENTS: Scholar at Zenzele High School (Goba) Hired Transport paid R60-00

In Vivo Study

Appendix C: Values for Span1, Span2, K_1, K_2 *and* Plateau *for modelled drugs.*

Drug	*Span1*	*Span2*	K_1	K_2	*Plateau*
CQ	4.413	8.820	0.0469	0.2708	0.497
SP	4.255	5.236	0.0488	0.2897	0.493
AQ	5.303	7.891	0.0568	0.3616	0.500
As	5.048	7.202	0.0548	0.3439	0.499
As-Mef	2.786	2.336	0.0376	0.1946	0.475
As-SP	3.986	4.642	0.0468	0.2717	0.491
Atova-P	1.658	0.8576	0.0278	0.1260	0.439
Co-A	1.292	0.5495	0.0239	0.1033	0.418
HF	2.505	1.903	0.0353	0.1771	0.468
Mef	2.298	1.612	0.0336	0.1645	0.463
PN	3.924	4.497	0.0463	0.2676	0.490

Table C.1. Variable values for each drug.