



**MALARIA CONTROL IN THE
LUBOMBO SPATIAL DEVELOPMENT AREA
:
A REGIONAL COLLABORATION**



August 2004

**Produced on behalf of the Regional Malaria Control Commission by the
MRC and UCT**



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OVERVIEW

The Lubombo Spatial Development Initiative (LSDI) is a programme by the governments of Mozambique, Swaziland and South Africa to develop the Lubombo region into a globally competitive economic zone, ensuring sustainable employment and equity in access to economic opportunity in the region. The geographic region targeted by this initiative is broadly defined as eastern Swaziland, southern Mozambique and north-eastern KwaZulu Natal, an area linked by the Lubombo mountains.

Malaria was identified as a critical deterrent to the development of the Lubombo region. This led to the creation of the Lubombo Malaria Control initiative, a cross-border collaboration aimed at the reduction of malaria throughout the LSDI area.

In July 1999 President Mbeki, President Chissano and His Majesty, King Mswati III signed the General Protocol which put in place a platform for regional cooperation and delivery. In October 1999 the Lubombo Malaria Protocol and tri-national malaria programme was launched. The Malaria Protocol of understanding was signed at ministerial level between the three countries in October 1999. The malaria component of the LSDI project is managed by the Regional Malaria Control Commission (RMCC), comprised of malaria control programme managers, public health specialists and scientists from the three countries. A comprehensive proposal outlining the LSDI malaria control programme and budgets was drawn up by the RMCC over the course of two three days meetings, funded by the development bank of SA and co-ordinated by the Medical Research Council.

The primary emphasis of the LSDI malaria control programme was to extend malaria control to southern Mozambique and thereby address a number of aspects central to increasing the effectiveness of malaria control in the two highest risk malaria provinces in South Africa and Swaziland. There was increasing consensus that even if malaria control measures were optimal in South Africa and Swaziland (with effective treatment and insecticides in place), the disease burden could only be further reduced by a regional approach to control. There is also increasing evidence that effective malaria control is a positive precursor to development with the situation prior to malaria control in South Africa supporting this view, given the well

documented negative effects of malaria on tourism and agricultural development in the 1930's. The LSDI malaria programme was targeted at creating a platform for development, the beneficiaries being communities in areas with the lowest socio-economic development in the region as well as tourism, business and governments. The effectiveness of the malaria control programme in the long-term will be assessed by the incidence of malaria over time in Mozambique as well as in the neighbouring malarious areas of South Africa and Swaziland. The success of intervention is not only measured using process (e.g. spraying and artemisinin-based combination therapy coverage) and biological markers (e.g. parasite prevalence rates, health facility patient numbers and mosquito vector reductions), but also by the effects on tourism e.g. bed occupancy, job creation and risk perceptions, in all three countries over the course of the 7 year period (2000 – 2007).

The malaria vector control component in Mozambique has been implemented in phases (Figure 1) starting with Zone 1, in 2000, which is the area extending from the KwaZulu-Natal border to Maputo. Zone 1A is the area surrounding the MOZAL Plant which introduced malaria control as part of their social responsibility campaign, implemented in 2001. Phase three, initiated in 2002, focussed on Zone 2A comprising part of the Boane District, and Zone 2 and 3 extending north along the Kruger National Park border, covering an area of over 20 000² Km. The contiguous malaria control area in the region now exceeds 100 000² Km.

Since effective malaria control requires both vector control and early effective treatment, the RMCC decided to extend their objectives to ensure that the best malaria treatment was introduced across the LSDI. Widespread use of artemisinin-based combination therapy (ACT) offers the benefits of not only improving cure rates, but, unlike other malaria treatments, of also directly decreasing malaria transmission and potentially slowing drug resistance. To optimise the synergistic effects of IRS and ACTs on reducing malaria transmission and thus disease burden, while minimising programme costs, the implementation of ACTs has been timed to follow the establishment of effective vector control.

KwaZulu Natal was the first Ministry of Health in Africa to implement an ACT malaria treatment policy, when it introduced Coartem in January 2001. The planned phased implementation of ACTs, which resulted in their introduction in Mpumalanga in 2003

and in two districts in southern Mozambique in 2004, is ahead of schedule and will ensure that ACTs will be in place throughout the LSDI region by 2006. These changes are being comprehensively assessed through the South East African Combination Antimalarial Therapy (SEACAT) evaluation, which is nested within the LSDI.

From the baseline malaria season of 1999/2000 to 2003/2004, these improvements in malaria control have resulted in dramatic reductions in malaria incidence of over 90% in KwaZulu-Natal, over 65% in Mpumalanga and over 90% in Swaziland. Parasite prevalence in children has decreased by over 88% in Zone 1 Mozambique. The documentation of process and outcome indicators has supported evidence based decision making within the LSDI and has played a significant role in informing policy makers across the African region.

The original objectives of the LSDI Malaria Control Programme are clearly being met. This has largely been achieved through the rare strength of partnership between MRC, UCT, Private partners and Governments (both National and Provincial) who are equally committed to and share a common vision for ensuring malaria control in the region, primarily through indoor residual spraying and ACT implementation, with ongoing monitoring and evaluation to support evidence based decision making.

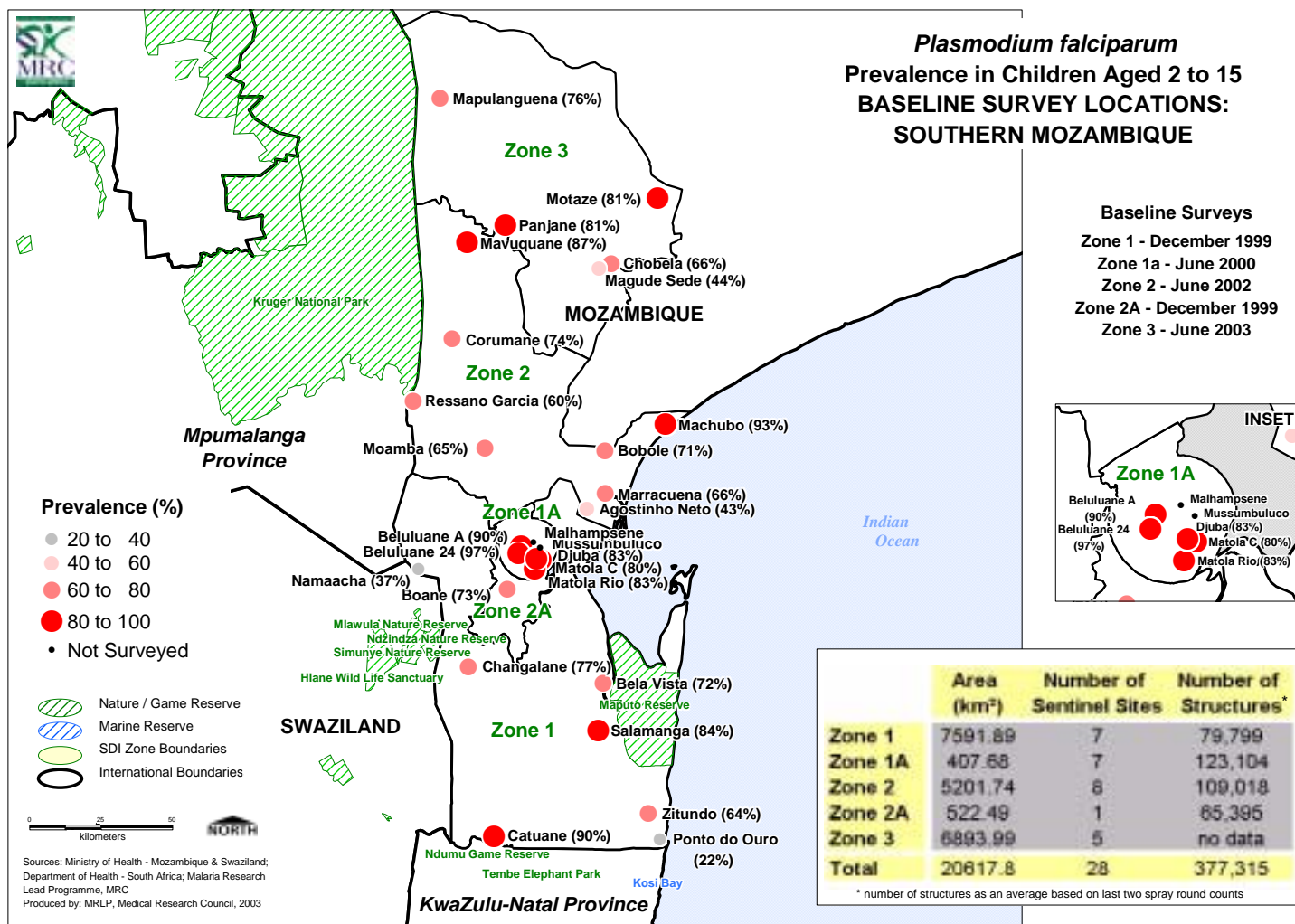


Figure 1. Malaria control Zones and baseline parasite prevalence rates at sentinel sites in Maputo Province, Mozambique.

This report is divided into two sections:

Section 1 reports on the overall objectives of the LSDI project, excluding drugs.

Section 2 reports specifically on the implementation of drugs and definitive diagnosis and associated research in the LSDI area.

Section 1.

Objective 1: To reduce malaria incidence in the border areas of South Africa and Swaziland from 250 per 1000 to less than 20 per 1000.

Swaziland

There was no evidence of any overall difference in risk of infection in children, compared to adults in any of the sites or years in which the parasite prevalence surveys were conducted (Odds Ratio 1.03, 95% CI 0.66 - 1.60, p=0.91). Survey results for adults and children were therefore combined and prevalence rates were low at the 4 sentinel sites ranging from 2-8% in 1999. By 2003 these were all <3% and in 2004 averaged 0.25%. The malaria incidence rates over the same period reduced dramatically by >90%.

South Africa

The border areas most influenced by the LSDI malaria programme are Komatipoort in Mpumalanga and Ingwavuma in KwaZulu-Natal. Prevalence surveys were in KwaZulu-Natal until the prevalence dropped below 10%. The prevalence at the three sentinel sites in KwaZulu-Natal ranged from 10 to 40% in 1999 with an average parasite prevalence of 19% in children and 17% in adults. By 2001 these parasite prevalence rates had dropped to below 5%. Malaria incidence rates reduced from the 1999/2000 baseline year to 2003/2004 by >90%.

Incidence data for the two localities are given in Figures 2 and 3. Although the scale of the disease differs in the different localities, the disease trends are similar. Significant reductions were made in these border regions once malaria control interventions had been implemented in adjacent areas in Mozambique. Indoor residual spraying was implemented in different years in the different zones in the LSDI area. Adjacent to Ingwavuma these measures were implemented in 2000/2001. In areas adjacent to Komatipoort, spray operations began in 2002/2003.

In subsequent years, the number of cases decrease markedly and has remained low ever since.

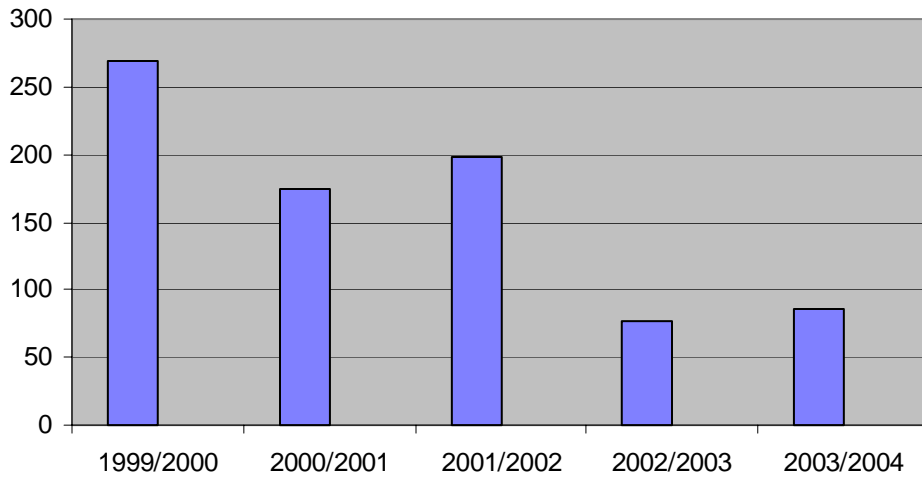


Figure 2. Malaria incidence data for Komatipoort..

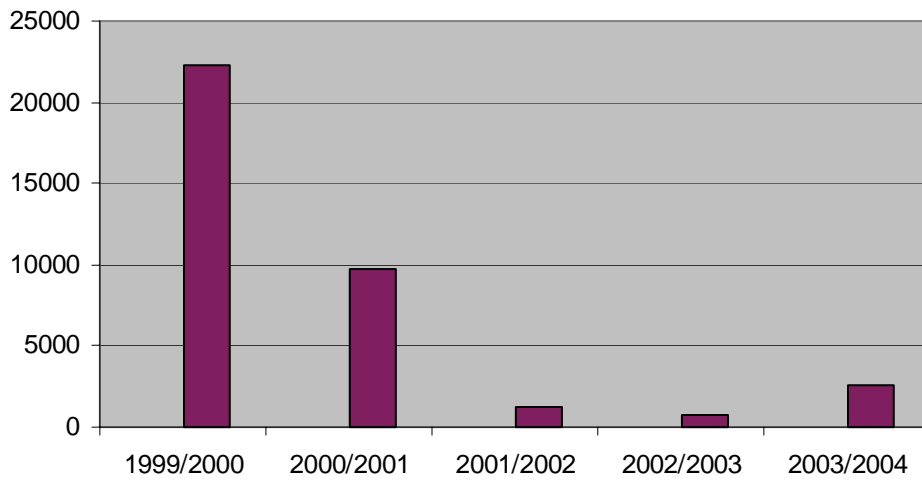


Figure 3. Malaria incidence data for Ingwavuma.

Objective 2: To reduce malaria infections from 625 per 1000 to less than 200 per 1000 within three year after the start of IRS in Maputo Province

A total of 9718 children between the ages 2 and <15 years were tested for parasitaemia at the sentinel sites in the 4 zones of the study area between December 1999 and June 2003.

In zone 1, child and adult prevalence surveys were conducted at all sites in the first survey round in December 1999. The average infection rate in the younger age group was 64 % as opposed to 30 % in adults (relative risk 2.12; 95% CI 1.87 - 2.41, $p < 0.0001$) with no evidence of heterogeneity in relative risks between sites (test for heterogeneity, $p = 0.90$). Surveys in all subsequent years, and in other sites, were restricted to children between the ages of 2 and under 15 years.

In zone 1 prevalence surveys were conducted in December 1999 and June 2000 before spraying began. Since there was no evidence of any difference in prevalence between these two surveys in children at the 7 sites ($p = 0.82$), site specific data from these two years were combined into a 2 year pre-spraying baseline and compared with prevalence values obtained from post spraying surveys undertaken in June 2001, June 2002, June 2003 and June 2004 after the first, third, fifth and seventh rounds of spraying. For zones 1A, 2 and 3, the prevalence surveys conducted in the years 2000, 2002 and 2003 respectively were used as pre-spraying baselines.

In zone 1 the average infection rate from all sites at baseline was 62 %, which reduced to 38% in June 2001, to 22% in June 2002 and 8% in June 2003 and remained low at 7.2% in June 2004 (Figure 4).

In zone 1A overall prevalence of infection at baseline in June 2000 was 86%. This reduced to 62% post spraying in June 2001, 36% in June 2002 and 18% in June 2003 and remained low at 20.8 % in June 2004.

In zone 2 overall prevalence of infection at baseline was 70% in June 2002, reducing to 34% in June 2003, after spraying and dropping to 29.8% in June 2004.

In Zone 3 the prevalence was 69.6% pre spraying and dropped to 58.4% after the first spray round

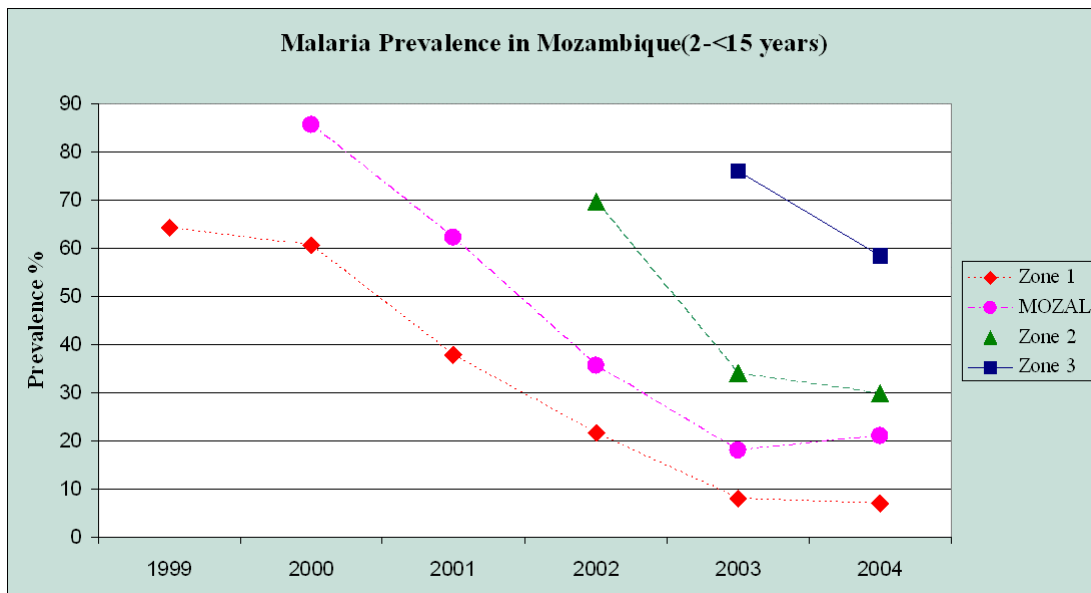


Figure 4. Malaria prevalence pre and post spray.

In Zone 2A baseline surveys in 1999 and 2000 showed a 76% prevalence, spraying was started in 2001 but due to financial constraints a permanent field officer was not assigned to the area and the spraying programme did not follow a fully structured plan as in the other areas until 2003 when funding allowed. Parasite prevalence decreased below baseline levels but not as dramatically as in other areas until 2004 when prevalence at 2 sites recorded 39% and 6% respectively.

Objective 3: To provide updated tourist information booklets containing definitive malaria risk maps and prophylaxis guideline

The tourism component of the project is progressing well. Surveys have now been completed in all SA provinces and are planned for expansion in Mozambique and Swaziland. A second revision and printing of the updated malaria and prophylaxis advice booklets are near completion for distribution to tourist facilities.

In the 1999/2000 malaria season, 18% of tourist facilities were in areas where 5 - 25 malaria cases per 1000 people were recorded, and 68% where in areas where the incidence was <5 per 1000 people. A major reduction in malaria cases was achieved by the 2002/2003 malaria season. None of the tourist facilities were in 5-25 malaria cases per 1000 people and 98% where in areas where < 5 malaria cases per 1000 people were recorded. The Greater St Lucia Wetland Park Authority has designated 10 development nodes within the park where local and international concerns will develop a wide range of tourist facilities from low-impact cabins to luxury hotels. The tourism data is increasingly influencing tourism policy. SA tourism is using the "Malaria Free" campaign to enhance its international marketing strategy (Sunday Tribune, June 2004). General Manager , Corporate affairs, Tourism KwaZulu-Natal stated "This Study (MRC) is a model of how tourism can benefit the people and the economy".

Objective 4: To develop a regional malaria control programme

In order to develop a regional malaria control programme, a number of different activities had to be implemented.

Regional management

The Regional malaria Control Commission (RMCC) is the co-ordinating and decision-making body of the LSDI programme. The RMCC is tasked with facilitating the extension of control to the Mozambique sector, developing a regional MIS, implementing effective treatment and regional monitoring and evaluation, developing human capacity and managing funding. The RMCC is accountable to the participating Ministries of Health, the Regional Coordinating Mechanism, its funders and the Research Ethics Committees that have approved the LSDI monitoring and evaluation programmes. The RMCC meets quarterly and the venue for meetings is rotational between countries. Decisions impacting on the project are made by consensus and supported by evidence on specific issues and the broad experience of its members, with all members having equal input. The RMCC is responsible for reviewing the progress of the project in the respective countries and finding solutions to problems that may occur. The RMCC then presents its findings and recommendations to Governments, funders and the Regional Co-ordinating Mechanism (RCM). The RCM

was set up as a GFATM requirement in 2003 to ensure good governance and appropriate expenditure of the Global Fund allocation.

The Medical Research Council, a South African institution set up to improve the nation's health status and quality of life through relevant health research, brought its well developed research support infrastructure to the table, including its Ethics committee, financial management systems, laboratories, staff and other management structures and international networks. This coupled to an experience base of co-ordinating large projects placed the MRC Malaria Research Programme in a position to undertake direct co-ordination of the day-to-day running of the programme on behalf of the RMCC, to provide secretarial, financial management, fund-raising and research support and to chair the RMCC. More recently the UCT has brought their services to the RMCC as well as the scientific monitoring and evaluation, and research training essential to malaria control.

Spray programme in southern Mozambique

Malaria vector control through indoor residual spraying (IRS) of houses was introduced in Zone 1 in Mozambique with bendiocarb at 400mg per m² in November 2000. IRS was undertaken twice annually. The programme was incrementally extended with insecticide being applied twice annually starting in Zone 1A in February 2001, Zone 2 in October 2002 and in Zone 3 in February 2004 (Table 1) The four zones comprise an area of 20617 km² covering 7 districts.

Table 1. Stepped wedge design of Indoor residual spraying intervention in Maputo province, Mozambique, with Bendiocarb at 400 mg per m²

Year	2000	2001	2002	2003	2004	Area in Km ²
	Cumulative Spray rounds					
Zone						
1	* 2	4 ^s	6	8	10	7591
1A	*	2	4	6	8	407
2			*2	4	6	5723
3				*	2	6893

^s spraying with Propoxur at 200mg per m²

Baseline pre spraying cross sectional prevalence survey

House spraying with DDT started in Swaziland in 1981. Spray dates during the study period were September to December each year from 1999 to 2003. The application rate was 2g per m².

House spraying with DDT in KwaZulu-Natal and Mpumalanga Provinces, South Africa started in the 1950's. In 1996 the policy changed to the exclusive use of a pyrethroid. After the emergence of pyrethroid insecticide resistance in the late 1990's, DDT spraying was reintroduced in KwaZulu Natal in February 2000, followed by a second round in June 2000 and in October for each of the subsequent years. The application rate was 2g per m². DDT was reintroduced for house spraying in Mpumalanga Province, South Africa, in October 2001.

All spraying was conducted throughout using Hudson expert pumps with 4001 nozzles. Spraying personnel and managers were trained in spraying techniques, safety measures and personal protection equipment appropriate to the insecticide.

KAP in all countries

A number of Knowledge, Attitude and Perception (KAP) were conducted in KwaZulu-Natal and Mpumalanga. KAP surveys were conducted in Mozambique in 1999 and 2003. However the results of these surveys were not utilised to identify gaps in the knowledge of the communities under study. During April – May 2004 KAP surveys were carried out at community level in all the malarious Provinces of South Africa and Swaziland to identify lack of knowledge, with the intent of designing IEC strategies towards development of focussed malaria education programmes. These two parts of the strategy have been completed and IEC is being implemented in school and communities to reinforce awareness and knowledge of malaria and its treatment. A KAP survey will once again be conducted in 2005 to determine the impact of the IEC on malaria knowledge.

GIS (see objective 5)

Gene flow

The emergence of drug resistance in the human malaria parasite, *Plasmodium falciparum*, is one of the major stumbling blocks in the control and eradication of malaria. Following the wide spread failure of chloroquine (CQ) as an antimalarial,

sulfadoxine-pyrimethamine (SP) became the first line drug of choice in most countries plagued with disease. Despite being a combination drug, resistance to SP developed and spread rather rapidly which has impacted negatively on the race to roll back malaria. To ensure that newer antimalarials have a longer life span it is essential to understand the rate and extend at which drug resistance is spread as well as all the factors that underpin the onset of drug resistance.

Sulfadoxine-pyrimethamine disrupts the folate biosynthetic pathway by interacting with two enzymes, dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) causing parasite death. Resistance to SP emerges as the result of point mutations in the genes coding for these enzymes, with a higher number mutations inferring a higher degree of resistance. To assess the level and extend of SP resistance we looked at four different point mutation sites in both the DHFR and DHPS genes which were thought to be associated with SP resistance using either sequence specific oligonucleotide probing and detecting polymerase chain reaction (PCR) dotblotting or nested PCR and restriction enzyme cleavage. Our preliminary results indicate that the peak in SP resistance in Southern Africa coincided with the emergence of two point mutations in the DHPS gene. The presence of three point mutations in the DHFR gene and two in the DHPS gene was also shown to be important predictors of SP failure.

Since point mutations are the main cause of drug resistance it was also essential to establish the evolutionary origin (gene flow or new mutations) of the drug resistance determinants as the origin would influence the measures taken to prevent/decrease the spread of resistance. Using microsatellite analyses we showed that SP resistance parasite from Tanzanian and Southern Africa share a common ancestor and thus it is likely that the spread of SP resistance in Africa is due to the spread of this lineage.

Malaria Vector Species and infection rates

Malaria vector numbers as monitored by daily exit trap catches from 147 traps at 28 localities show dramatic reductions after spraying and in Zone 1 where spraying was started in 2000 there are >99% reductions both the *Anopheles funestus* group and *Anopheles gambiae* complex mosquitoes caught. Reductions in the other Zones ie 1A, 2 and 2A were in the range of 87-98% for *Anopheles funestus* group and 96-99% for the *Anopheles gambiae* complex.

An. gambiae complex

A total of 6178 *An. gambiae s.l.* were caught in the window traps prior to spraying and 737 post spraying, which constitutes a 93.5% reduction when corrected for trapping nights. Three member species of the *An. gambiae* complex group (*An. arabiensis*, *An. merus* and *An. quadriannulatus*) were identified in all zones in Mozambique from both pre-spray and post-spray window trap collections. Prior to the commencement of spraying, *An. arabiensis* made up 84% of total *An. gambiae s.l.* mosquitoes identified with *An. merus* and *An. quadriannulatus* at 12% and 4% respectively. (Total number of *An. gambiae* complex identified prior to spraying =817).

Numbers of *An. gambiae s.l.* decreased rapidly after the first spray round and have continued to remain low. Of the sample of mosquitoes from the post spraying collections and subject to specific species identification, *An. arabiensis* numbers decreased proportionately (36% of the total) with the other members of the complex becoming proportionately more prevalent; *An. merus* 55% and *An. quadriannulatus* 9%. (Total number of *An. gambiae* complex identified post spraying =520).

An. funestus group

A total of 11217 *An. funestus* group. were caught in the window traps prior to spraying and 2069 post spraying, which constitutes a 90.5% reduction when corrected for trapping nights. Prior to spraying, four member species of the *An. funestus* group were identified, *An. funestus* (95%), *An. rivulorum* (<1%), *An. parensis* (<1%) and *An. leesoni* (4%). (Total number of *An. funestus* group identified prior to spraying =802)

Post-spraying results show a proportional decrease in the number of *An. funestus* (65%) and a relative increase in the other member species; *An. rivulorum* 28%, *An. vaneedeni* 3%, *An. parensis* 3% and *An. leesoni* 1%. *An. vaneedeni* was found in one location only, Zitundo, in the south-east of Zone 1. (Total number of *An. funestus* group identified post spraying=527).

Large variations in mosquito numbers and in species composition exist between zones and between sentinel sites within zones.

Plasmodium sporozoite rates

Molecular analysis to determine sporozoites rates was carried out on all positively identified mosquitoes. Sporozoite rates varied widely between zones and between pre and post-spraying. The pre-spraying rate for *An. gambiae s.l.* ranged from 0,84% to 10,9% (n=784) and post-spraying rates ranged from 0-1,22% (n=471)

An. arabiensis was found to be the major vector of the *An. gambiae* complex. *An. merus* was implicated as a minor vector in the eastern areas of Zone 1 where they were the predominant species.

The pre-spray sporozoite rate for *An. funestus s.s.* ranged between 4.69% and 5.28% (n=763). Post-spray rates ranged between 0 and 2.7%. (n=339) No other *A. funestus* member species was found to be infected.

Resistance in mosquitoes

Surveys were undertaken in December 1999, prior to implementation of IRS to ascertain which vector species occurred in Maputo Province and their susceptibility to the insecticides used in IRS. The initial proposal was to use pyrethroids for IRS in Mozambique, however the discovery of high levels of pyrethroid resistance by *Anopheles funestus* required the choosing of an alternative insecticide.

Insecticide resistance monitoring is an ongoing component of the monitoring and evaluation of the IRS programme.

Capacity development

The foundation of a successful, efficient and effective spraying programme is optimally trained staff at every level. Experience in this regard was lacking in Mozambique, and training was therefore a key priority before a spraying programme could be introduced. It was also conducted on an ongoing process once spraying started.

Training of field staff, whether spray operators or supervisors, followed a similar pattern i.e. 85% practical and 15% theory. However, supervisors received more in-depth training on environmental hazards, toxicity, first aid and safe handling/disposal of insecticides. Training of supervisors and spray persons has

taken place each year. The Mozambican programme managers assisted Mpumalanga in training their spray operators in 2002.

Training was extended to include intervention assessment and in this regard, window-trap caught mosquitoes were morphologically identified in Mozambique, and residual efficacy bio-assays carried out. The latter required the maintenance of an insectary and the ability to undertake both susceptibility and biochemical resistance testing which are increasingly being done in the country and will lead to a postgraduate degree. Training has been undertaken to equip field entomologists with the necessary research techniques, field staff to use global positioning system (GPS) receiver hand-held units, office staff in the use of the MIS and insectary staff in Maputo. Sonia Casimiro obtained her MSc degree through the University of Natal in 2003 on insecticide resistance in Mozambique. Intervention assessment with regard to development has been assessed through various studies investigating perceptions of tourists and tourist facility operators to malaria and its impact on this sector. Francois Maartens has completed an MSc degree through the University of Natal in 2003 on Perceptions of malaria risk in KwaZulu-Natal Province.

Evaluation of direct impact

Cross sectional parasite surveys were performed by the respective country malaria control programmes, at sentinel sites in the four Zones in Mozambique to which malaria control was extended and in South Africa and Swaziland at sentinel sites within 10 kilometres of the Mozambique border (Zone 1). HRP-2 antigen tests (ICT™ and Kat Medical) were used to assess prevalence of infection. Giemsa stained thick bloodsmear films were collected from a sub-sample of 1155 survey respondents from the Mozambican sentinel sites and examined microscopically by skilled microscopists for validation of the antigen test. At each of the 26 Mozambican sites at least one survey was conducted prior to the intervention to provide estimates of pre-spraying baseline prevalence of infection. A random sample of 120 individuals was taken for each survey at each sentinel site; sample size was powered to detect a significant change in prevalence based on an assumption of 20 % reduction in prevalence post intervention. Initial parasite prevalence surveys were conducted in the respective Zones in Mozambique in December 1999 (Zone1), June 2000 (Zone 1 and 1A), June 2002 (Zone 2) and June 2003 (Zone 3) with post intervention assessment in June of each subsequent year. Parasite prevalence surveys were carried out in KwaZulu-

Natal in December 1999, June 2000, February and June 2001. Swaziland surveys were done in December 1999, and in June of each year thereafter. All age categories were sampled, with the exception of the surveys in Mozambique where this was only done in December 1999 and confined thereafter to children 2 to <15 years of age.

Objective 5: To develop a regional GIS based malaria information system

Malaria Information Systems (MIS) were developed and implemented for each of the partner-sectors with modifications being made on an ongoing basis. This computerised system allows the input, management and output of malaria case data which is used for both management and research purposes. It includes a spatial component using a geographic information system (GIS) which is being customised to minimise end-user skill requirements and optimise access to the different data sets. The data collected during routine operations and entered into the MIS consists of both in- and out-patient data of confirmed and clinically diagnosed malaria cases. The input screens mirror the data collection forms and the automatic-linking and drop-down list minimising data entry errors.

Pre-designed outputs are provided in the form of maps, graphs or tables (i.e. number of can refills per week per person). This allows problems to be identified and addressed on an ongoing basis.

Spatial data has been collected for the region and includes administrative boundaries, population, health facility locations, towns and other relevant information. New sources are continually sought to ensure that current data at appropriate scales are provided.

The information systems provide for the management of two types of malaria-related data:

1. Malaria case data, and
2. Information relating to the malaria control activities, namely indoor residual spraying.

Malaria is a notifiable disease in all three countries requiring the recording of individual case details. Where testing capabilities do not exist, summary case records are kept of patients presumed to be infected with the malaria parasite.

In South Africa and Swaziland all cases are definitively diagnosed and definitive diagnosis has recently been implemented in Mozambique as part of the Global Fund initiative. Definitively diagnosed cases are essential to provide an overview within the country of the effect of malaria control activities as well as to monitor the regional effects of the LSDI malaria control programme. This is to be accomplished by ensuring that each MIS captures core data for comparative purposes while also allowing for the inclusion of local variables. Once definitive diagnosis has been implemented in Mozambique, incidence data (i.e. number of cases per annum) will be used to monitor control efforts when the malaria prevalence rates drop below 10%.

An important factor identified prior to the implementation of the spraying programme was the necessity to adequately supervise the spray operations. Due to the vast area to be sprayed, supervision of spray operators' activities on a daily basis was virtually impossible. A fourth generation relational database (MS Access) was therefore designed as an information repository for all spraying activities, and the data generated from computerized reports made it possible to evaluate productivity and spraying performance on an ongoing basis. Quality control was undertaken by the malaria control programme managers of Swaziland, KwaZulu-Natal and Mpumalanga during each spraying round. Information regarding the indoor residual spraying activities is entered into the MIS to manage and monitor the efficacy of control in Swaziland, Mozambique, and the provinces of KwaZulu-Natal and Mpumalanga in South Africa. Data is entered onto spray-cards during routine spraying activities by the spray operators and then entered on a weekly basis into the MIS thereby allowing the insecticide application rates, number of structures sprayed and pump refills to be calculated per spray operator. This allows problems to be identified and addressed on an on-going basis.

Both components of the MIS (malaria case data and spray data) were designed in consultation with the Malaria Control Programme teams in the respective countries to ensure inclusion of the users requirements.

Section 2

SEACAT evaluation

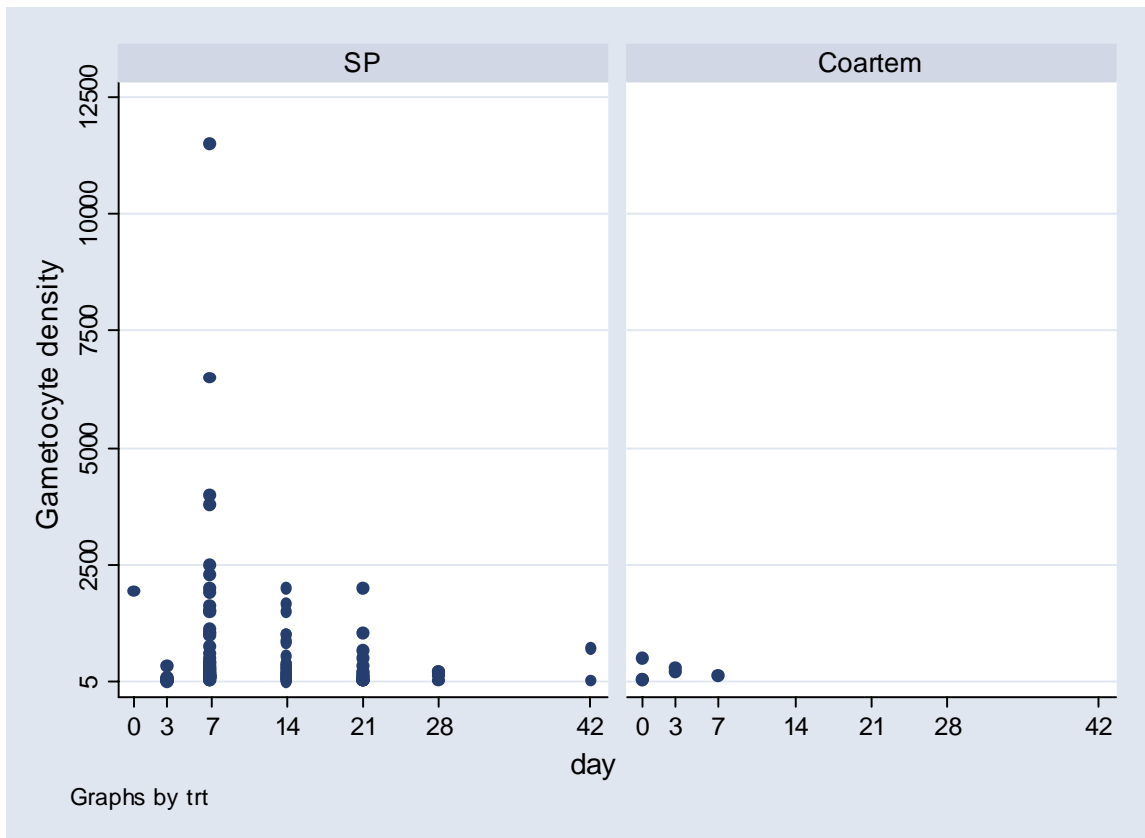
OBJECTIVE 1: To determine the therapeutic efficacy of sulfadoxine-pyrimethamine (SP), artesunate-SP and artemether-lumefantrine (AL) to provide an evidence base to support ACT selection.

A total of thirteen in vivo studies (four RCTs, 9 open label studies) have successfully been completed with 42-day follow up in 8 study sites between 2000 and 2003, defining the therapeutic efficacy of sulfadoxine-pyrimethamine (n=642), artesunate plus sulfadoxine-pyrimethamine (n=207) and artemether-lumefantrine (n=100). A randomised controlled trial comparing the therapeutic efficacy of artesunate plus SP vs SP monotherapy is currently ongoing in Magude and Boane, southern Mozambique in which a further 186 patients have been enrolled thus far. Adequate clinical and parasitological response (ACPR) following SP treatment ranged from 13% in KwaZulu Natal in 2000 to 96% in Limpopo in 2001-2002. Artemether-lumefantrine (AL) had an ACPR rate of 99% in KwaZulu Natal in 2001, while artesunate-SP (AS-SP) had an ACPR of 95% in southern Mozambique in 2003 and 96% in Mpumalanga in 2004. These findings led to the rapid implementation of AL as first line treatment in KwaZulu Natal, and the selection of AS-SP for Mpumalanga and Namaacha.

OBJECTIVE 2: To determine gametocyte carriage following treatment with SP, artesunate-SP and artemether lumefantrine.

Gametocyte carriage rates were highest following SP treatment (particularly in areas of low intensity transmission and/or SP high resistance), and lowest following artemether-lumefantrine treatment. In KwaZulu Natal, gametocyte prevalence decreased from 57% following SP monotherapy, to 2% following artemether-lumefantrine [RR 28.5 (CI 7.16-113.97)]. The median gametocyte area under the time curve decreased significantly from 420 to 0 gametocytes/ μ L per person week (Figure 5).

Figure 5: Scatter plot of non-zero gametocyte densities over time by treatment in KwaZulu Natal



OBJECTIVE 3: To describe the safety of first line antimalarial treatment in each of the study sites.

In South Africa, the feasibility and value of four different methods for safety surveillance, to determine the safety profile of antimalarial therapy and the factors contributing to adverse clinical outcomes in patients with malaria, were assessed. The four detection methods used were (1) a spontaneous reporting system at hospitals and outpatient facilities following intensive training of health care personnel to report adverse events following ANY treatment; (2) a confidential enquiry into malaria-related deaths (n=219); (3) a follow-up home visit by a representative of the Malaria Control Programme of all patients treated for malaria at health facilities (n=1909); and (4) inpatient interviews and chart review of patients recently exposed

to antimalarials (n=160). Three of the four methods provided useful information on the safety of combination antimalarial therapy and different drug-related risks associated with this therapy.

To date, 174 deaths have been investigated in the confidential enquiry in all 3 provinces (69 in Mpumalanga province, 35 in Kwa Zulu Natal and 70 in Limpopo province). Of these 82 have already been reviewed by an international expert review panel and the remaining cases will be reviewed at a final expert panel which is scheduled to take place from July 26-28, 2004. Key system failures included delayed treatment seeking, inadequate assessment and monitoring of patients during hospitalisation, improper fluid management and lack of access to high care facilities.

The spontaneous reporting system facilitated reporting of adverse reactions, particularly hypersensitivity reactions and treatment failures (n=29). The malaria control program follow-up of all malaria cases notified allowed evaluation of patient adherence to therapy and identified patients with adverse outcomes after treatment at a health facility. Until March 2004, 423 patients in Kwa Zulu Natal and 1486 in Mpumalanga were followed up. In Kwa Zulu Natal, 2 patients (0.5%) were reported to be still sick at follow-up of whom one was non-compliant. Of those questioned about their compliance, 94% were documented to have been compliant. In Mpumalanga, 4 patients (0.3%) were reported to be still sick at follow-up, of whom 2 were non-compliant; 99% of cases followed up were documented to have been compliant. More updated data from this method are currently being analysed.

The inpatient interview and chart review of patients recently exposed to antimalarials was the least valuable method; it was labor-intensive, costly, and produced information on treatment failures, system errors, and irrational drug use only in small numbers of patients. 27/120 treatment failures associated with SP monotherapy were identified in the Mpumalanga hospital, while 4/40 AL treatment failures were noted in the KwaZulu Natal hospital.

As no pharmacovigilance system was in place in southern Mozambique, a pilot programme evaluated the feasibility of implementing a spontaneous reporting system in Namaacha and Matatuine. The adverse drug reaction (ADR) form,

reporting guidelines, and training material were developed with the participation of local healthcare providers. An initial and follow up training session were attended by 27 and 24 health professionals (medical doctors, technicians, nurses, clinical pharmacist), respectively. On site technical support visits occur each quarter. To date 43 ADRs have been reported, of which 23 were associated with antimalarial use (chloroquine (13); SP (7); artesunate plus SP (2); quinine (1)). Skin reactions accounted for the vast majority of the reports (37/43). There were eight reactions that reporters considered serious, two of which were associated with antimalarials (convulsions following quinine, skin reaction following artesunate plus SP).

In addition to the above surveillance methods, adverse events were monitored for in each of the SEACAT *in vivo* therapeutic efficacy studies. Results up to 2002 have been presented in previous reports, and are summarized in Tables 2 and 3. The higher frequency of Adverse Events (AEs) following SP treatment may reflect more rapid relief of malaria symptoms by artemether-lumefantrine, better tolerability of artemether-lumefantrine or that clinicians or patients in KwaZulu Natal report adverse events less frequently despite the same training and supervision.

Table 2: Preliminary analysis of adverse events (AEs) and Adverse Drug Reactions (ADRs) in 2002 *in vivo* Therapeutic Efficacy studies

Site	Treatment	N	TOTAL AEs	Serious AEs	Probably attributable
KwaZulu Natal	Artemether-lumefantrine	100	17	0	1 Malaria recrudescence / reinfection 4 GIT ADRs 1 Urticaria
Mpumalanga	SP	152	120	9 Malaria 1 Anaemia	15 Malaria
Mozambique	SP	150	126	1 Malaria	48 Malaria recrudescence / reinfection 2 Pruritis 6 GIT ADRs

During the randomized controlled trial comparing SP with artesunate plus SP in Namaacha and Catuane in 2003, 115 adverse events were reported, of which 3 were considered serious and 38 were considered possibly or probably related to study drugs.

Table 3: Preliminary analysis of adverse events (AEs) and Adverse Drug Reactions (ADRs) in 2003 *in vivo* Therapeutic Efficacy studies

Site	Treatment	N	TOTAL AEs	Serious AE	Possibly / Probably attributable
Mozambique	SP	62	55	N=1 Hospitalisation for cholera on day 21 Causality: unlikely	4 chills/fever 4 GIT AE 3 nervous system AEs 1 arthralgia 2 anaemia 4 respiratory AEs 1 other
Mozambique	ASSP	66	60	N=2 (hospitalisation for severe malaria on day 2) Causality: probable	7 GIT AEs 3 nervous System AEs 3 respiratory AEs 2 arthralgia 2 anaemia 2 other

OBJECTIVE 4: To describe antimalarial drug management, availability and use to determine current strengths and weaknesses, and identify interventions to improve drug management.

Weaknesses in drug management were identified in all sites studied, and attempts have been made to address each of these. SP and quinine prices were 6-13.5-times higher than the international median price in South Africa, while artemether-lumefantrine was procured at 2.5-times the international median price. Stockouts were only discovered in 2 sites: first line treatment was out of stock in study healthcare facilities for 164 days in KwaZulu Natal in 2001, and 258 days in Namaacha during 2002. Improved drug management resulted in ACT stockouts for only 2 days in KwaZulu Nata and no stockouts in Namaacha in 2004. Immediately following AL implementation in KwaZulu Natal, only 60.8% of patients with uncomplicated malaria were prescribed recommended therapy, but within 4 months this had increased to 93.4%. Inventory control systems were not in place in 40% of public healthcare facilities sampled in Mpumalanga in 2001, and thus the malaria control programme accepted the responsibility of monitoring antimalarial availability and use while pharmaceutical services are being strengthened.

Objective 5: To describe community perspectives on malaria treatment seeking and adherence.

Nineteen focus group discussions have been held with groups of 8-12 female household heads and detailed household surveys have been completed in 2314 households (12429 household members) in five study sites. These studies confirmed a generally high awareness to seek malaria treatment early, and self reported antimalarial adherence of 93-95%. There was some dissonance between household survey and FGD findings regarding patient adherence, with a few FGD participants indicating that they would stop treatment once symptoms resolved and save medication for future episodes. These household surveys and focus group discussions are currently being analysed in detail, and their findings will be used to improve malaria treatment seeking and adherence.

Objective 6: To describe the costs of malaria treatment to the public sector provider, and to determine the cost effectiveness of ACT implementation.

During 2001, the per patient costs of malaria treatment with monotherapy varied significantly between study sites, and level of healthcare facility. In South Africa, the per patient costs of treating uncomplicated malaria was higher at hospital outpatient facilities (US\$ 17.05-32.21) than clinics (US\$ 4.60-13.1). These outpatient costs were markedly higher than in Mozambique (US\$ 1.40-2.94). Costs per inpatient day ranged from US\$ 20.43-73.33 in South Africa and US\$ 15.90-27.80 in Mozambique. Personnel and antimalarial treatment costs contribute the bulk of the costs in South Africa, while capital and personnel costs are the major contributors in southern Mozambique.

In KwaZulu Natal, the recurrent and capital costs for malaria case management in Manguzi sub-district were compared at nine clinics and one sentinel rural district hospital, before and after artemether-lumefantrine (AL) replaced SP as first line treatment. After accounting for the role of concurrent improvements in vector control, it was conservatively estimated by means of an expert international Delphi survey that 36% of the decline in outpatient cases and 46% of the decline in inpatient admissions were attributable to AL. Although AL is considerably more expensive than SP, the resulting improved cure rate, and reduced gametocyte carriage (and thus lower malaria transmission) resulted in an estimated US\$ 201,065 cost saving in 2002 alone for the sub-district studied, with a population of approximately 300 000 at risk of malaria. A decision tree model demonstrated that AL was significantly more cost effective than SP, with the average cost per life saved being US\$ 18 with AL compared with US\$ 158 with SP, in the KwaZulu Natal context.

Objective 7: To develop sustainable capacity to conduct comprehensive evaluations of malaria treatment policy within the southern African region, and particularly within the participating Ministries of Health and Malaria Control Programmes.

Local training and capacity building has and will continue to underpin each component of the SEACAT evaluation. The training to date includes 229 data collectors who are supported by regular on-site supervision and quality assurance, two Good Clinical Practice (GCP) monitors who are provided with ongoing training

and supervision by the SEACAT GCP manager, over 400 healthcare providers trained on the rational use of ACT in Kwazulu Natal, Mpumalanga, and Namaacha / Catuane, over 100 healthcare providers instructed on reporting adverse drug reactions, 22 clinicians and malaria control programme officers trained in conducting confidential enquiries into malaria related deaths, the participation of 27 SEACAT investigators / MOH staff in 5 short courses / workshops and the registration of six SEACAT investigators and four MOH staff in postgraduate studies (3 PhD; 4 Masters; 3 Honours). More importantly, the participating Ministries of Health and their Malaria Control Programs are primarily involved and responsible for conducting baseline evaluations, and subsequently the implementation and evaluation of a change in malaria treatment for uncomplicated malaria at district or provincial level. This is essential for ensuring that the performance of these evaluations can be locally sustained.

The SEACAT evaluation has been highly successful in meeting each of its seven ambitious study objectives in seven study sites and in facilitating the implementation of artemisinin-based combination therapy as first-line malaria treatment policy at district or provincial level in three countries in southern Africa. KwaZulu-Natal province, South Africa, was the first Ministry of Health in Africa to introduce an ACT malaria treatment policy, when it implemented artemether-lumefantrine as first line treatment in January 2001, following the SEACAT evaluation detecting high levels of SP resistance in 2000. In Mpumalanga province, South Africa, SP remained highly effective, so artesunate plus SP was implemented as first line treatment in January 2003. Similarly, Namaacha district in southern Mozambique implemented artesunate plus SP in April 2004. Limpopo province, South Africa will be implementing artemether-lumefantrine in October 2004. ACTs will be implemented in Swaziland by end 2004, and their phased implementation is planned across 7 districts in southern Mozambique between 2004-2006.

Scientific manuscripts published to date

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13. Bredenkamp BLF, Sharp BL, Durrheim DN, Barnes KI Failure of Sulfadoxine - pyrimethamine in treating Plasmodium falciparum malaria in KwaZulu Natal province. South African Medical Journal 2001; 91: 970 - 972
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Scientific manuscripts submitted for publication include:

1. Malaria morbidity and mortality following implementation of artemether-lumefantrine as first-line treatment of uncomplicated disease in KwaZulu-Natal, South Africa.
2. Therapeutic efficacy of sulfadoxine-pyrimethamine for treating uncomplicated Plasmodium falciparum malaria five years after implementation in Mpumalanga province, South Africa.

Scientific manuscripts in preparation

1. Malaria control in the Lubombo Spatial Initiative area of Mozambique, South Africa and Swaziland.
2. Malaria vectors, infectivity and control in southern Mozambique.
3. Knowledge, attitudes and perceptions in regard to malaria and health seeking behaviour in the LSDI area.

Thesis Completed

1. Casimiro, SLR (2003) Susceptibility and resistance to insecticides among malaria vector mosquitoes in Mozambique. MSc, University of Natal, Durban.
2. Maartens F (2003) Malaria risk in the Lubombo Spatial Development Initiative Area: A Perceptual and Scientific Analysis. MSc, University of Natal, Durban.

Comprehensive websites are maintained

www.malaria.org.za

www.Lubombomapping.org.za

Appendix 1 GFATM Annual Target Sheet

Attachment 1 to Annex A Intended Program Results and Budget

Country: Mozambique, South Africa and Swaziland
Program Title: Malaria Control in the Lubombo Spatial Development Initiative area
Grant Number: MAF-202-G01-M-00
Disease: Malaria
Principal Recipient: Medical Research Council
Period: July 1, 2003 to June 30, 2004

A. Main Program Objectives, Key Indicators and Intended Results/Targets

Main Programme Objective	Key indicators	Area	Baseline	Year Target	Achieved	Data Source
1. Malaria transmission to be significantly reduced	Parasite Prevalence At 28 sentinel sites in Mozambique (n=number of parasite prevalence samples per Zone)	Zone 1 (n=840)	64%	20%	7.2%	Yearly surveys conducted in June 2003/04
		Zone 1A (n=600)	84%	30%	20.8%	
		Zone 2A (n=120)	79%	30%	22.1	
		Zone 2 (n=960)	70%	60%	29.8	
		Zone 3 (n=480)	2003	60-90%	59	
	Malaria incidence in border areas % reduction (Total case numbers per province, district and area)	KwaZulu-Natal	>100/1000	10/1000	12.5/1000	MIS
		Mpumalanga	>100/1000	10/1000	<3/1000	
		Swaziland	>40/1000	10/1000	<3/1000	
	Facility based malaria mortality	All areas	0.4-3%	20% reduction	In progress	Hospital register data capture system in place.
	Daily vector exit trap catches at number of sentinel sites	All areas	80 traps	108	27 Sites, 138 traps	Fitted traps
Number of structures sprayed	All areas	0	253 000	818 479	IRS database	
Number of trained spraypersons and refresher training	All areas	NA	240	367	Training schedule	

	Insecticide purchased	All areas	NA	12 000 kg	42 630 kg	All funders
2. To ensure effective case management	ACT purchased	Zone 1 Namaacha, Catuane	0	UA	100%	See procurement document
	%Health Care Facilities (15x HCF) with <10 days ACT stockout	Zone 1	0	30%	100%	Monthly stock review
	% HCF using Treatment guideline (15 x HCF) (n=14 250 treatment doses)	Zone 1	0	50%	100%	Facility survey
	In vivo 42 day study	Zone 1 (3 sites)	Data collection	3 completed	3 completed	Modified WHO 1996 method

Main Programme Objective	Key indicators	Capacity	Baseline	Year Target	Achieved	
3. Human Resource capacity	Personnel hired and trained	Spray persons	0	200	367	
		GIS/MIS	3	3	4	
		IRS managers	5	6	6	
4. Monitoring and Evaluation	Drug safety monitoring system in place		-	Spontaneous ADR reporting System in place	Spontaneous ADR reporting System in place	
	Regional MIS		-	System in place	System in place	
	Annual Insecticide resistance monitoring			ongoing	ongoing	