LUBOMBO

Spatial Development Initiative

Annual Report 2006

Compiled on behalf of the Regional Malaria Control Commission

Table of Contents

OVERVIEW

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 service delivery. The Lubombo Spatial Development Initiative (LSDI) is a trilateral 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 an area linked by the Lubombo mountains and broadly defined as eastern Swaziland, southern Mozambique and north-eastern KwaZulu Natal.

Malaria was identified as a major 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 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), a core group of experts, comprising of malaria control programme managers, public health specialists and scientists from the three countries.

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.T he 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 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).

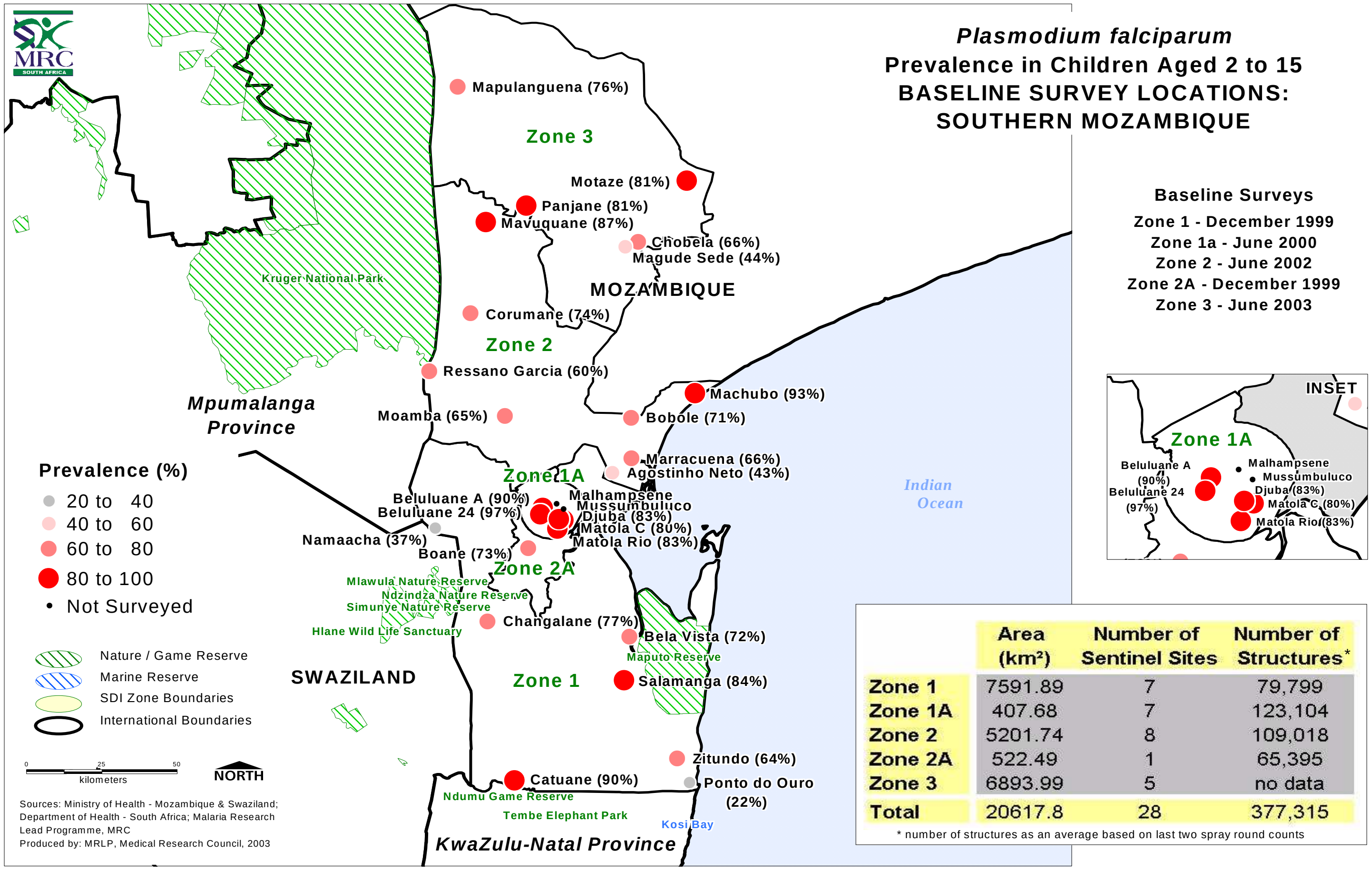
The malaria vector control component in Mozambique has been implemented in phases (Figure 1) starting with Zone 1, in 2000, which is the area extending from the KwaZulu-Natal border to Maputo. Zone 1A is the area surrounding the MOZAL Plant which introduced malaria control as part of their social responsibility 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 20 000^2 Km. The contiguous malaria control area in the region now exceeds 100 000^2 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 2005/2006, these improvements in malaria control have resulted in dramatic reductions in malaria incidence of over 99% in KwaZulu-Natal, over 70% in Mpumalanga and over 83% in Swaziland. Parasite prevalence in children has decreased by over 94% 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.



	Area (km²)	Number of Sentinel Sites	Number of Structures*
Zone 1	7591.89	7	79,799
Zone 1A	407.68	7	123,104
Zone 2	5201.74	8	109,018
Zone 2A	522.49	1	65,395
Zone 3	6893.99	5	no data
Total	20617.8	28	377,315

* number of structures as an average based on last two spray round counts

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 LDSI project, excluding drugs.

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

SECTION 1: Malaria Vector Control

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 population.

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 2005 averaged 0.25%. The malaria incidence rates over the same period reduced dramatically by >90% to 0.17%.

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 2005/2006 by >99%.

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 decreased markedly and has remained low ever since.

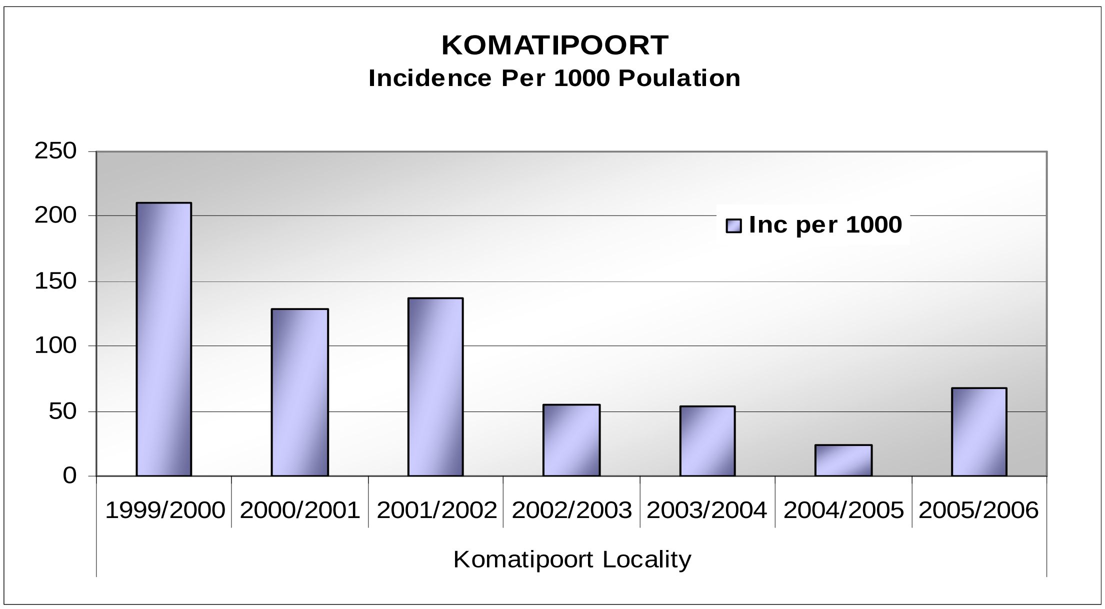


Figure 2. Malaria incidence data for Komatipoort.

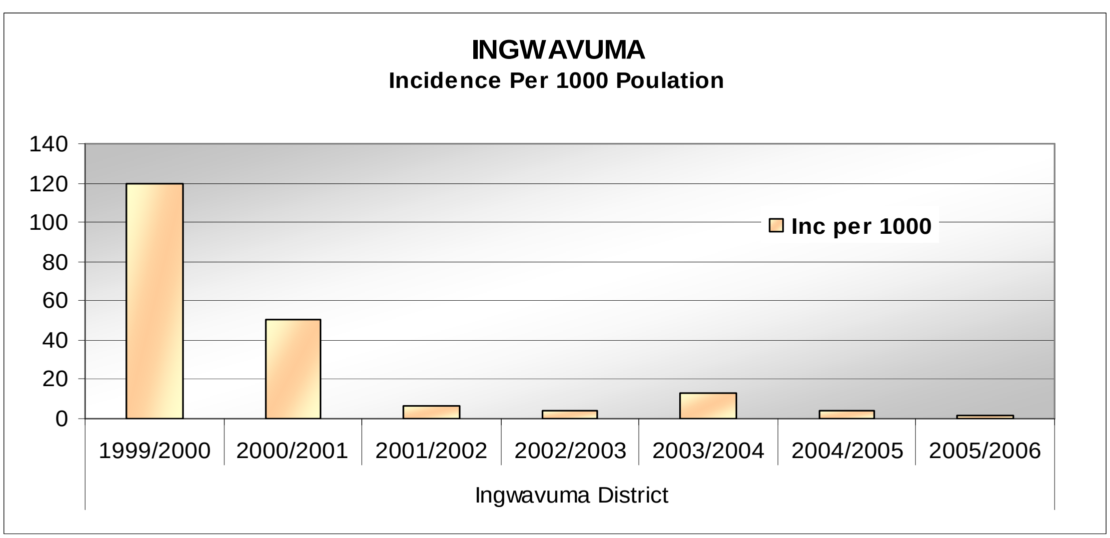


Figure 3. Malaria incidence data for Ingwavuma.

OBJECTIVE 2: To reduce malaria infections from 625 per 1000 to less than 200 per 1000 within five years after the start of Indoor Residual Spraying (IRS) in Maputo Province.

A total of 15943 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 2006 (Figure 4).

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 annually in June for the period 2001 - 2006 after the first, third, fifth and seventh and 10th 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. The reductions obtained are reflected in Table 1.

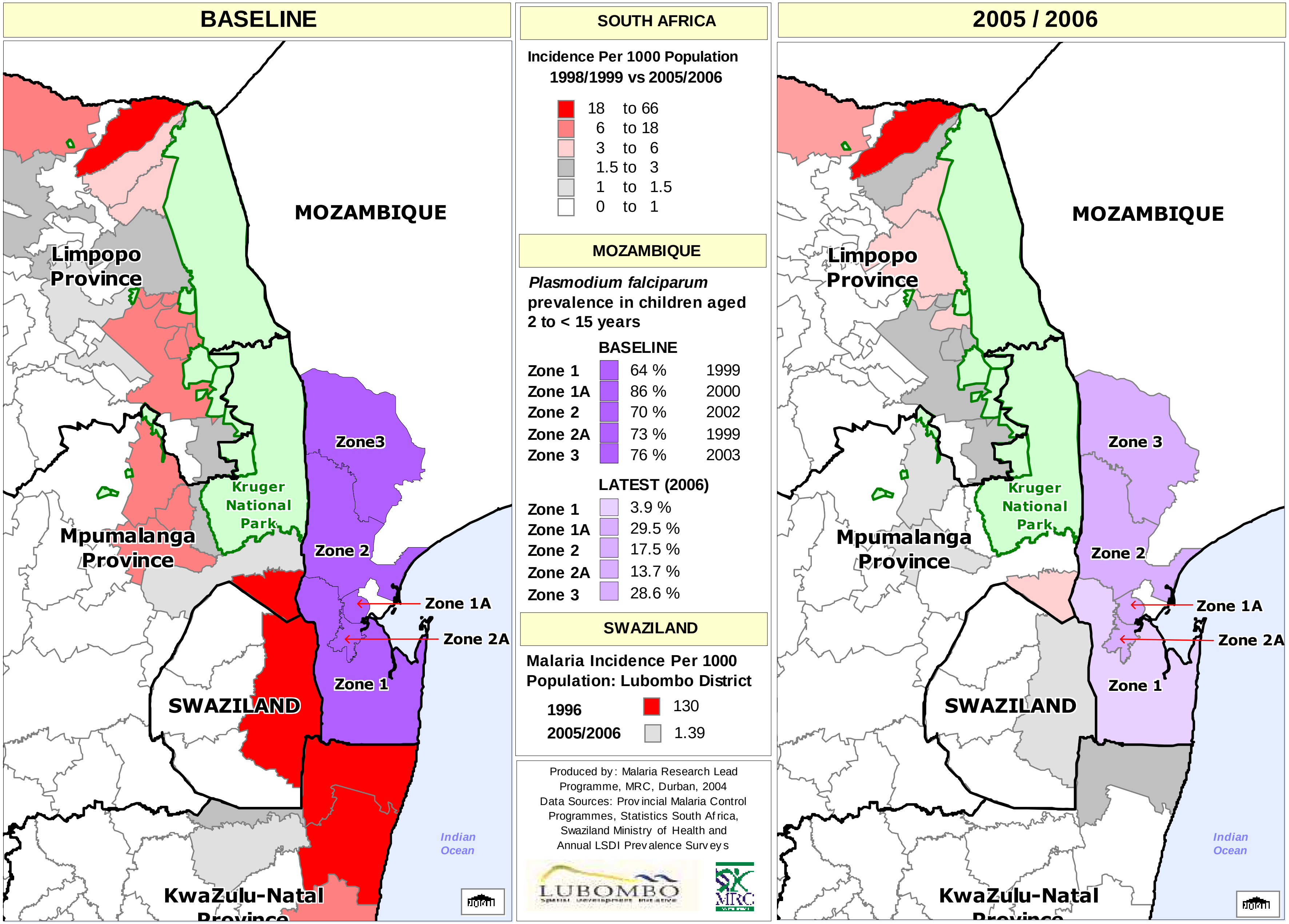


Figure 4. Sentinel sites for annual parasite prevalence surveys.

In Zone 2A baseline surveys in 1999 and 2000 showed 73 and 79% prevalence, respectively. 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 became available (GFATM) (Figure 5). Parasite prevalence hereafter decreased as dramatically as in other areas.

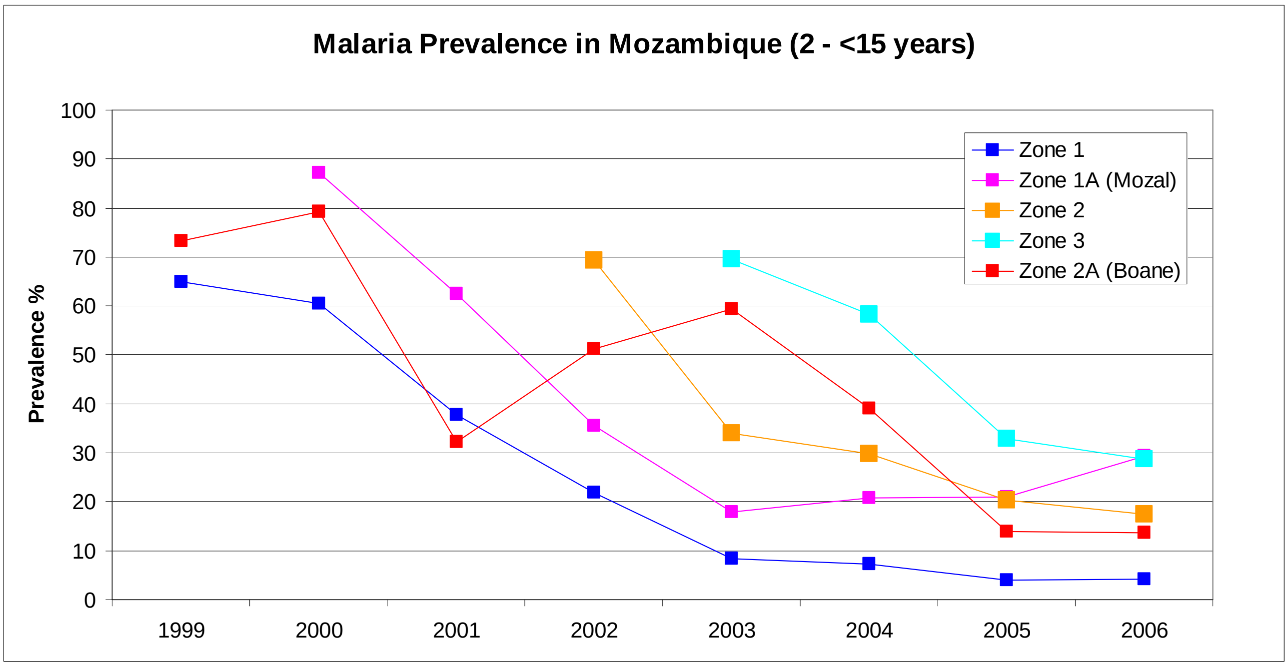


Figure 5. Malaria prevalence pre and post spray (1999 – 2006).

Table 1. Results of the prevalence survey in Maputo Province showing annual reductions.

	1999	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**RELATIVE RISK ***	**EEFICACY ****
Zone 1	64.82	60.39	37.79	21.84	8.45	7.27	3.91	4.3	0.07	93.37
Zone 1A		87.27	62.5	35.5	17.87	20.83	21.04	29.46	0.34	66.24
Zone 2A	73.27	79.17	32.31	51.28	59.32	39.17	13.96	13.68	0.19	75.27
Zone 2				69.42	34.07	29.87	20.32	17.53	0.25	74.75
Zone 3					69.53	58.38	32.98	28.62	0.41	58.84

* Relative Risk = prevalence in 2006 / baseline prevalence

** Efficacy = (baseline prevalence - prevalence in 2006) / baseline prevalence

Baseline Prevalence

Prevalence in 2006

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.

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 were 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 where 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 Goverments, 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 m^2 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 2) The four zones comprise an area of 20617 km^2 covering 7 districts. Since 2005, DDT has also been used for indoor residual spraying.

Table 2. Stepped wedge design of Indoor residual spraying intervention in Maputo province, Mozambique, with Bendiocarb at 400 mg per m^2

Year	2000	2001	2002	2003	2004	2005	2006	Area (km^2)
<u>Zone</u>	**Cumulative Spray Rounds**							
1	* 2	4[§]	6	8	10	11	12	7591
1A	*	2	4	6	8	9 / 10	11	407
2			*2	4	6	7 / 8	9	5723
3				*	2	4	6	6893

[§] spraying with Propoxur at 200mg per m^2

[#] 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 2005. The application rate was 2g per m^2.

House spraying with DDT in KwaZulu-Natal and Mpumalanga Provinces, South Africa started in the 1940'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 m^2. 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 three countries

A number of Knowledge, Attitude and Perception (KAP) were conducted in KwaZulu-Natal and Mpumalanga. KAP surveys were conducted in Mozambique in 1999, 2003 and 2005. 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. Follow-up surveys were conducted in all malaria affected provinces in 2006 to determine the impact of the IEC on malaria knowledge.

Prevalence of Antimalarial Resistance Markers and Gene flow

The emergence of antimalarial drug resistance in the human malaria parasite, *Plasmodium falciparum*, is one of the major stumbling blocks in the control and eradication of malaria. As a result of wide spread chloroquine resistance, sulfadoxine-pyrimethamine (SP) was adopted as the first line drug of choice in most countries plagued with disease. Unfortunately resistance to SP developed and spread rapidly, limiting the therapeutic lifespan of this drug. In response to the rapid emergence of resistance to most antimalarial monotherapies, the WHO advocated that artemisinin combination therapy (ACT) become standard antimalarial policy. In 2004 the ACT, artesunate plus SP (AS-SP) replaced chloroquine as first line therapy in Maputo Province of Mozambique. To ensure that this newer antimalarials has a long 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 prior to and following the introduction of AS-SP we examined eight point mutation sites in the *dhfr* and *dhps* genes, associated with SP resistance using either sequence specific oligonucloetide probing and detecting polymerase chain reaction (PCR) dotblotting or nested PCR and restriction enzyme cleavage.

Our results revealed that the peak in SP treatment failure in Southern Africa coincided with the emergence of two point mutations in the *dhps* gene. Additional we showed that the presence of three point mutations in the *dhfr* gene and two in the *dhps* gene were important predictors of SP therapeutic failure. Following the removal of SP drug pressure within the LSDI region (initially due to the introductions of ACTs in KwaZulu-Natal), we found that the prevalence of the two *dhps* resistance markers began to decline and by 2004 had reached baseline levels. However our preliminary results indicate that following the introduction of AS-SP, the prevalence of these two *dhps* markers has began to rise again. Although the current prevalence levels of the *dhps* mutations are relatively low, close monitoring of these markers must be maintained to ensure that SP remains an efficient partner drug to artesunate.

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 in both the *Anopheles funestus* group and *Anopheles gambiae* complex mosquitoes caught. Reductions in the other Zones i.e. 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 6196 *An. gambiae s.l*. were caught in the window traps prior to spraying and 1238 post spraying, which constitutes a 96.5% 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 11% and 5% respectively. (Total number of *An. gambiae* complex identified prior to spraying =1048).

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 (42% of the total) with the other members of the complex becoming proportionately more prevalent; *An. merus* 53% and *An. quadriannulatus* 5%. (Total number of *An. gambiae* complex identified post spraying =969).

***An. funestus* group**

A total of 11173 *An. funestus* group. were caught in the window traps prior to spraying and 2337 post spraying, which constitutes a 96.7% 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* (3%). (Total number of *An. funestus* group identified prior to spraying =855).

Post-spraying results show a proportional decrease in the number of *An. funestus* (70%) and a relative increase in the other member species; *An. rivulorum* 20%, *An. vaneedeni* 3%, *An. parensis* 2% and *An. leesoni* 5%. *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=753).

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=989) and post-spraying rates ranged from 0-1,0% (n=684).

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 2.4% and 6.3% (n=809). Post-spray rates ranged between 0 and 3.5%. (n=538) 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 and is the subject of a PhD study..

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 mangers have assisted Mpumalanga in training their spray operators since 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. Two students have completed MSc degrees through their work on the LSDI and one of them is registered at Liverpool School of Tropical Medicine for a PhD.

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 about 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 South African provinces of KwaZulu-Natal and Mpumalanga. Data is entered onto spray-cards during routine spraying activities by the spray operators, and then entered weekly 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. All components of the MIS were designed in consultation with the Malaria Control Programmes in each country to ensure inclusion of the users requirements.

SECTION 2 : Malaria Case Management in the LSDI

SEACAT Evaluation

Improvements in malaria case management have well exceeded targets set for the LSDI (Table 3).

Table 3: Summary of progress against target indicators by Year 3 of the LSDI

Indicator	Targets	Actual Result
Number of public healthcare facilities using ACT's as first line treatment of uncomplicated malaria	30	53
% of target public healthcare facilities with no reported stockouts of either ACT's or RDT's	80%	>98%
Number of public healthcare facilities routinely using RDT's to confirm malaria diagnosis	35	85
Proportion of definitively diagnosed cases appropriately treated with ACT	90%	117%
Drug efficacy monitoring	2	2
Number of districts with an established pharmocovigilance system	4	7
ACT drug efficacy level	90%	97.7%
Clinical personnel receiving inservice training	100	348

Achieving this large scale deployment of artemisinin-based combination therapy and rapid diagnostic malaria tests at more healthcare facilities than initially planned within the defined budget has been made possible by the marked reduction in malaria case load following the effective community based indoor residual spraying and widespread use of ACTs, and by limiting treatment to only definitively diagnosed malaria cases. Efficient management of drug and RDT supplies and use through extensive training and supervision has minimised stockouts and wastage.

Significantly Reducing Malaria transmission

This objective is being achieved through community based indoor residual spraying with effective insecticides and through wide-spread use of artemisinin-based combination therapy (ACT) as first line treatment. The artemisinin derivatives, such as artesunate and artemether, have been selected specifically for their ability to reduce gametocyte carriage. Gametocytes are the stage of the *Plasmodium falciparum* life cycle responsible for transmission of malaria from the human host to the mosquito vector (Figure 6). Gametocyte carriage is being monitored in the *in vivo* studies of therapeutic efficacy, all of which have shown significant reduction in gametocyte carriage in the ACT arm when compared with the SP monotherapy arm.[i,ii]

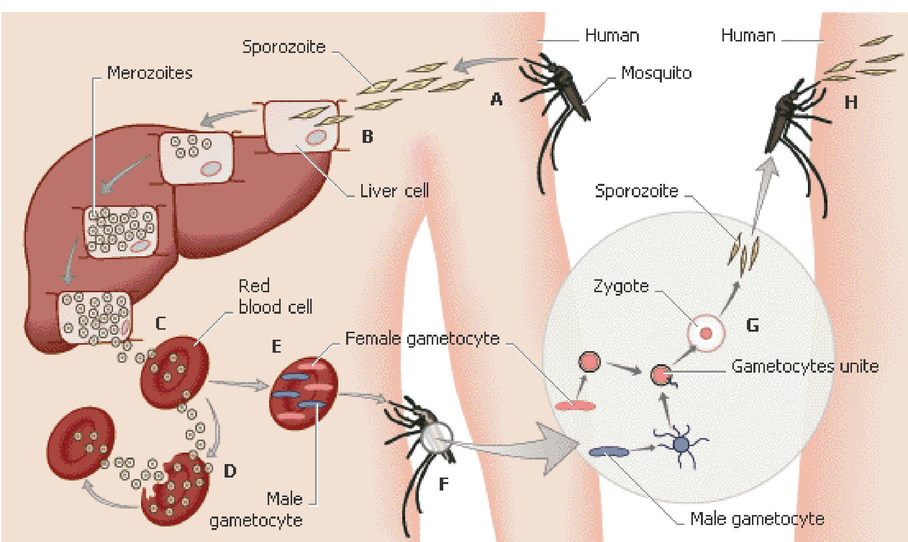


Figure 6: *Plasmodium falciparum* lifecycle (©Microsoft Corporation www.encarta.msn.com)

Ensuring effective malaria treatment

There has been phased implementation of artemisinin-based combinations since 2001 when KwaZulu Natal was the first Ministry of Health in Africa to introduce artemether-lumefantrine as therapy as first line treatment policy. In January 2003, Mpumalanga introduced an artesunate plus SP treatment policy and in October 2004 Limpopo introduced an artemether-lumefantrine treatment policy. Each of these policy changes were entirely funded by the South African Department of Health.

In southern Mozambique, the phased district level implementation of artesunate plus SP has been supported financially by the Global Fund to fight AIDS, tuberculosis and malaria. This has been achieved in all 53 public sector health posts and health centres in Namaacha (March 2004), Matutuine (July 2004), Boane (January 2005), Marracuene (July 2005) Magude (November 2005) and Moamba (April 2006) districts. This well exceeds the LSDI target of 30 healthcare facilities. As a result, between September 2005 and August 2006 45 160 patients with confirmed malaria were treated in Maputo Province with artesunate plus SP, which has a cure rate of over 95% in all sites studied[1].

Rapid diagnostic tests are now being used for definitive diagnosis in all health centres and health posts in all LSDI districts including all of Matola district (Figure 7). Although only part of Matola district falls within the borders of the LSDI area, it is essential that malaria case management interventions are implemented simultaneously across all public sector healthcare facilities within a given district. Thus, an agreement was reached with the Mozambican Ministry of Health (MOH) whereby the LSDI fund, distribute and manage RDTs, while the MOH supplies ACTs throughout Matola district. This successful model of additionality bodes well for the sustainability of effective case management in the future. RDTs have also been introduced at selected community health posts to encourage patients with malaria to seek further treatment at a facility with ACTs. In total, RDTs are now routinely available at 85 public healthcare facilities, well ahead of the LSDI target of 35 healthcare facilities.

The drug and RDT management systems implemented by the LSDI have reduced stock-outs to a minimum. In the past year (September 2005 – August 2006) only 1 of 83 facilities stocking RDTs and 4 of 53 facilities stocking ACTs recorded any stockouts, compared with the target of <20%. All stockouts were of short duration. The number of RDT used and the proportion of clinically suspected malaria cases that are RDT positive varies by district (Figure 8). During the past year (September 2005 – August 2006), 130 439 RDTs have been used to confirm malaria diagnosis in 44 871 cases. Patients in whom the malaria test is negative should benefit from more prompt management of the actual cause of their illness.

The efficacy of ACTs within the LSDI has been closely monitored through in vivo therapeutic efficacy studies with 6 week follow up. These have shown the ACTs to be highly effective across all study sites, and to be significantly more effective than monotherapy.[1,2] However, it has been noted with concern that despite patients receiving directly observed treatment with the internationally recommended dose of SP, drug levels achieved in pre-school children are approximately half those in adults. [iii] Younger children treated with sulfadoxine-pyrimethamine are therefore doubly disadvantaged by lack of immunity and lower drug concentrations. This late recognition of the critical impact that age has on SP drug levels, despite widespread use for decades, has raised the question of whether other vulnerable populations are similarly at risk of being under-dosed. The LSDI has thus initiated two studies on antimalarial drug levels achieved in pregnant women in Mozambique in 2006. Studies of the therapeutic efficacy of artemether-lumefantrine will be started in Limpopo and Mpumalanga in 2007.

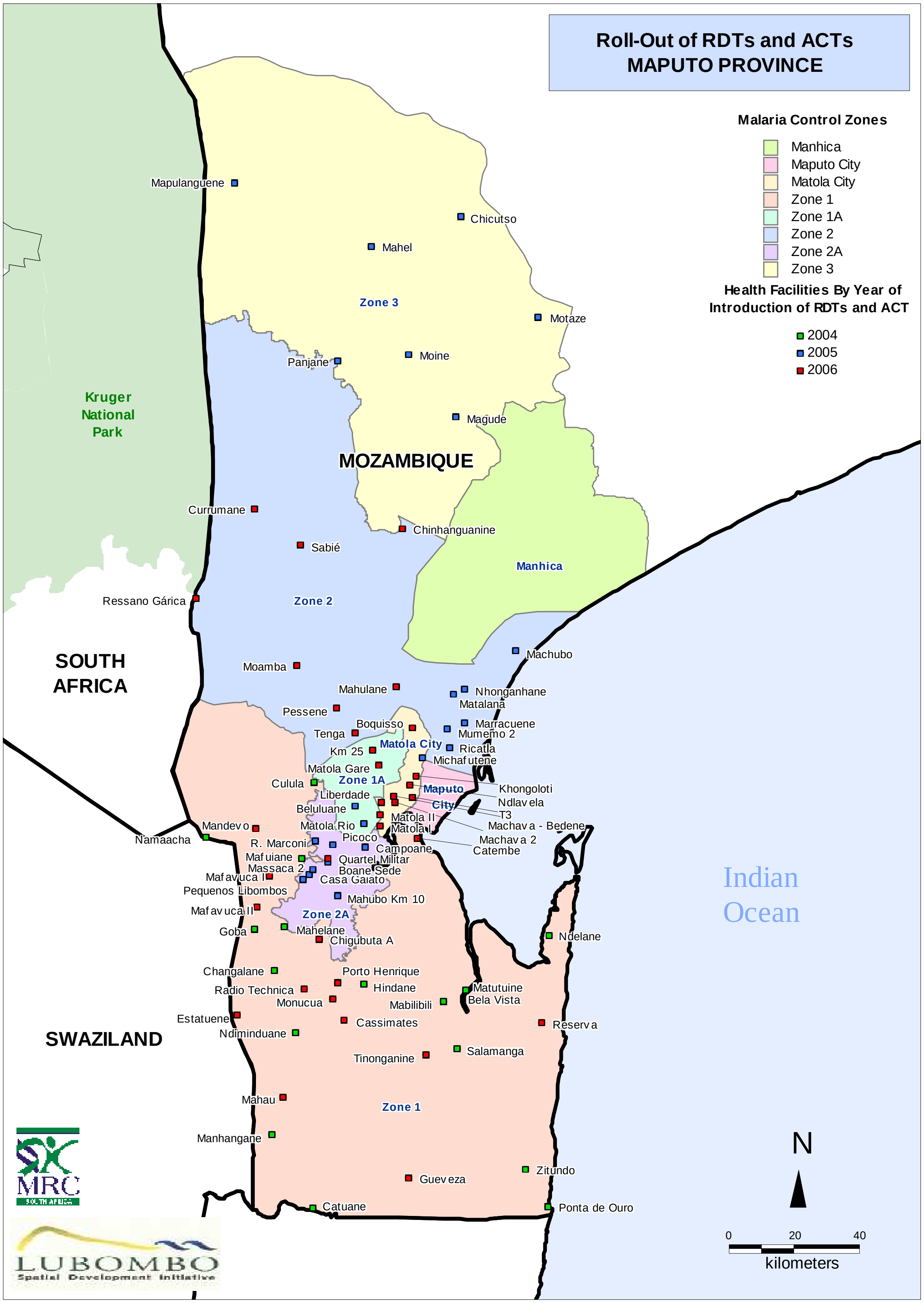


Figure 7. Public sector health facilities in Maputo Province where ACTs and RDTs have been deployed.

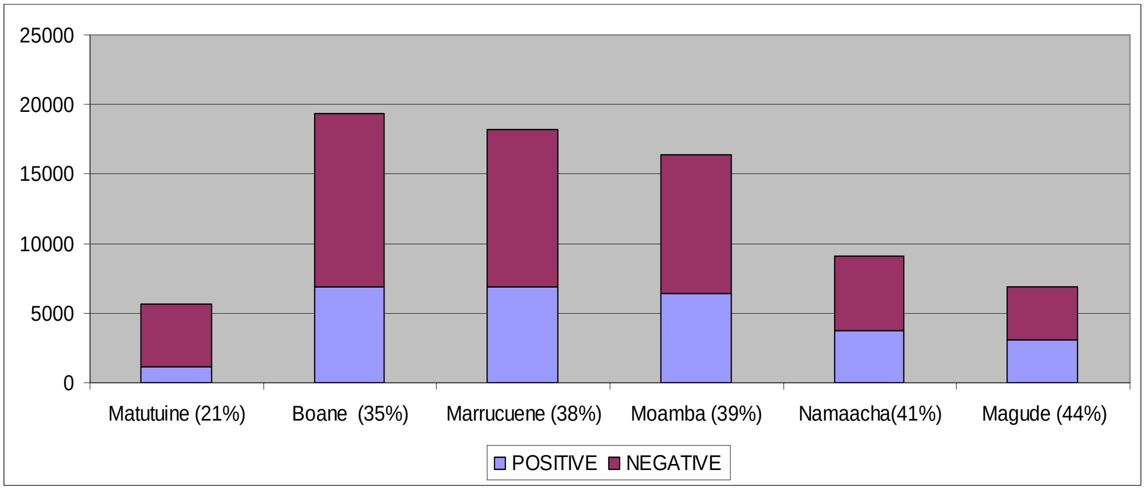


Figure 8: Number of RDTs used and Proportion of clinically suspected malaria cases that are rapid test positive, by district (January – July 2006).

Building human resource capacity

Human resource capacity has been built in both the implementation of ACTs and RDTs and in monitoring and evaluation of these interventions. Effective ACT and RDT deployment required strengthening of the healthcare infrastructure including in service training of all healthcare providers at target healthcare facilities. Introductory training includes drug and RDT management, malaria diagnosis using RDTs (and microscopy), assessment of disease severity, treatment guidelines, indications for referral, record keeping and pharmacovigilance. This training is supported by regular on site supervisory visits and the provision of malaria treatment guidelines, drug management manual, pharmacovigilance handbook and adverse drug reaction reporting forms. To date, at least 348 healthcare workers have participated in this integrated training programme, well in excess of the target of 100.

Academic training of core contributors to the LSDI is provided when the RMCC identifies a specific gap in knowledge or skill that is needed to meet the objectives of the LSDI. There are currently 15 professionals receiving such academic training at Diploma, Masters or PhD level, with 7 from Mozambique and

8 from South Africa. Fields of further training include public health, tourism, drug and insecticide resistance, and drug safety.

Monitoring and evaluation

Each component of the LSDI is comprehensively monitored, as reported above. This monitoring and evidence based policy is supported by the Geographic and Malaria Information Systems that are now fully functional in all LSDI study sites.

References

1. LSDI annual report 2005
2. Barnes KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, Dlamini SS, Tsoka J, Bredenkamp B, Mthembu DJ, White NJ, Sharp BL. Effect of Artemether-Lumefantrine Policy and Improved Vector Control on Malaria Burden in KwaZulu-Natal, South Africa. PLOS Medicine 2005;2(11):e330
3. Barnes KI, Little F, Smith PJ, Evans A, Watkins WM, White NJ. Sulfadoxine-pyrimethamine pharmacokinetics in malaria: paediatric dosing implications. Clinical Pharmacology and Therapeutics (in press).

Scientific manuscripts published to date

1. lSharp BL, Kleinschmidt I, Streat E, Maharaj R, Barnes KI, Durrheim DN, Ridl FC, Morris N, Kunene S, la Grange JJP, Mthembu J, Seocharan I, Maartens F, Martin C and Baretto A. Regional collaboration for enhanced malaria control – Mozambique, South Africa and Swaziland. *American Journal of Tropical Medicine and Hygiene* (in press)
2. Barnes, KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, Dlamini SS, Tsoka J, Bredenkamp B, Mthembu DJ, White NJ, Sharp BL. Effect of Artemether-Lumefantrine Policy and Improved Vector Control on Malaria Burden in KwaZulu-Natal, South Africa. PLOS Medicine 2005;2(11):e330
3. Maharaj, R, Jotham, DJ & Sharp, BL. 2005. The impact of the reintroduction of DDT on malaria transmission in KwaZulu-Natal, South Africa. South African Medical Journal. 95 (11).
4. Roper C, Pearce R, Nair S, Sharp B, Nosten F and Anderson T. 2004. Science (20) 35: 1124.
5. Maharaj, R., Cassimiro, S., Mthembu, S.D. and Sharp, B.L. (2003) The residual life of bendiocarb: a field based evaluation from Mozambique. Journal of Medical Entomology. 40 (5)
6. Roper C, Pearce R, Bredenkamp B, Gumede J, Drakely C, Mosha F, Chandramohan D and Sharp B (2003) Antifolate antimalarial resistance in southeast Africa: a population-based analysis. The Lancet, 361, pp 1174-1181.
7. Booman M, Sharp BL, Martin CL, Manjate B, La Grange K and Durrheim DN. (2003) Enhancing malaria control using a computerized management system in southern Africa. Malaria Journal 2:13, 1-5.
8. Conteh L, Sharp BL, Streat E, Barreto A and Konar S. (2003) The Cost and Cost-Effectiveness of Malaria Vector Control by Residual Insecticide House-Spraying in Southern Mozambique: a Rural and Urban Analysis. Tropical Medicine and International Health, 9 (1), 125-132.
9. Muheki C, McIntyre D, Barnes K. Artemisinin-based combination therapy

reduces expenditure on malaria treatment in KwaZulu Natal, South Africa. Trop Med Int Hlth 2004 (in press).

10. Stepniewska K, Taylor WRJ, Mayxay M, Smithuis F, Guthmann JP, Barnes K et al. The *in vivo* assessment of antimalarial drug efficacy in falciparum malaria; the duration of follow up. Antimicrob Agents Chemother. 2004;

11. Durrheim DN, Williams HA, Barnes KI, Speare R, Sharp BL, 2003. Beyond evidence: a retrospective study of factors influencing a malaria treatment policy change in two South African provinces. Critical Public Health 13 (4); 309-330.

12. Kachur SP, Abdulla S, Barnes K, Mshinda H, Durrheim DN, Kitua A, Bloland P. Mothers, malaria and resistance. Trop Med Int Health 2001; 6: 324-325.

13. Barnes KI, Folb PI 2004. Measuring Resistance to malaria treatment (Editorial). S Afr Med J; 94(1): 36-7.

14. Durrheim DN, Sharp BL, Barnes KI, 2001 Sentinel malaria surveillance - merely research or indispensable public health tool? Editorial . South African Medical Journal 2001; 91

15. Mabuza A, Govere J, Durrheim D, Mngomezulu N, Bredenkamp B, Barnes K, Sharp B 2001 Therapeutic efficacy of sulfadoxine - pyrimethamine for uncomplicated plasmodium falciparum malaria three years after introduction in Mpumalanga Province, South Africa. South African Medical Journal 2001; 91: 975-77 ·

16. 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

17. Baker L, Barnes K 2001 New antimalarial treatment in KwaZulu Natal South African Medical Journal 91 (5): 358-9.

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 maintained

www.malaria.org.za

www.Lubombomapping.org.za