REPORT

LUBOMBO SDI- MALARIA CONTROL PROGRAMME

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Abstract
The Lubombo Spatial Development Initiative (LSDI) malaria control programme was officially inaugurated by the 3 country, ministerial signing of a protocol of agreement, during October 1999. The geographic area targeted by this initiative is broadly defined as Eastern Swaziland, Southern Mozambique and North-eastern KwaZulu Natal. This manuscript reports on malaria control in the border areas of South Africa and Swaziland and Maputo Province, Mozambique.

Baseline surveys were carried out to assess malaria parasite prevalence at 3 sites in Swaziland, 3 in KwaZulu Natal Province, South Africa and 7 sites in Maputo Province Mozambique. House spraying in Swaziland was done using DDT, KwaZulu-Natal re-instituted the use of DDT in 2000 and a house spraying programme was initiated in Maputo Province, Mozambique using Bendiocarb in October 2000.

DDT has been used in Swaziland since 1984 and is highly effective with parasite ratios below 10% being recorded. Kwazulu-Natal Province re-introduced DDT following the discovery of pyrethroid resistance in *Anopheles funestus* and this resulted in a statistically significant decrease in parasite ratios, after 2 spray rounds, to less than 10%. Statistically significant reductions in parasite ratios were recorded at 6 of the 7 sentinel sites in Maputo Province following the first round of house spraying with Bendiocarb.

The data indicate a regional reduction in malaria incidence as a direct result of the extension of effective regional vector control.

Introduction

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. The geographic area targeted by this initiative is broadly defined as Eastern Swaziland, Southern Mozambique and North-eastern KwaZulu Natal and is linked by the Lubombo mountains.

In July 1999 President Mbeki, President Chissano and His Majesty, King Mswati III signed the General Protocol which puts in place a platform for regional cooperation and delivery. In October of 1999 the Lubombo Malaria Protocol and tri-national malaria programme was launched. In December of 1999 the World Heritage Convention Act was promulgated and the Greater St Lucia Wetlands Park inscribed on the World Heritage Convention list. In June 2000 the three countries signed the Lubombo Transfrontier Conservation and Resource Area Protocols (TFCA).

Although the malaria control project addresses a number of aspects central to increasing the effectiveness of malaria control in the two highest risk malaria provinces in South Africa and those in Swaziland, a primary emphasis was to extend malaria control to Southern Mozambique. There is increasing consensus that even if malaria control measures are optimal in South Africa and Swaziland (i.e. effective drugs and insecticides in place), disease incidence can only be further reduced by a regional approach to control.

The highest risk malaria areas in South Africa (Sharp & le Sueur 1996) and Swaziland all border Mozambique.

There is evidence, that malaria control is a positive precursor to development (Gallup and Sachs, 1999) and the situation prior to malaria control in South Africa supports this view (Sharp and le Sueur 1996,), given the well documented negative effects of the disease on tourism and agricultural development in the 1930's before control measures were implemented (le Sueur *et al.*, 1993). The malaria programme is targeted at creating a regional platform for development and the beneficiaries are local communities, tourism, business and government. These communities include some of the lowest levels of socio-economic development in the region (Sharp et al 2001).

The Lubombo Spatial Development Initiative (LSDI) malaria control programme was officially inaugurated by the 3 country, ministerial signing of a protocol of agreement, during October 1999. The signing of this protocol legally constituted the Regional Malaria Control Commission (RMCC), a commission comprised of malaria scientists, control and public health specialists from the three countries. The control programme is based on comprehensive technical proposals developed by the RMCC who report to a Tri-Lateral Ministers Committee comprised of ministers from the three countries. The RMCC were of agreement that to attain the objectives of control as outlined by the commission and for the necessary skills transfer required for sustainability of the programme in Mozambique, would require an initial 5 year commitment to the project. The malaria control programmes in South Africa and Swaziland are funded directly by the respective governments. Infra structural and staff salaries to manage the project are largely covered by existing institutions and governments. Funding for the project for the first two years (2000/2001) has been by The South African Business Trust, The Department of Health in South Africa and the Ministry of Health in Mozambique.

This manuscript reports on malaria control in the border areas of South Africa, Swaziland and Maputo Province, Mozambique.

Methods

Figure 1 outlines the sentinel sites in the three countries (Existing control) and Zone 1 in Mozambique (New control area**)**, the area to which malaria control was extended.

Cross sectional parasite surveys were carried out in Mozambique, Swaziland and South Africa by the respective country malaria control programmes. Hrp-2 antigen tests (ICT^{TM} and Kat Medical) were used to assess prevalence of infection. Figure 1 shows the sentinel sampling sites in the 3 countries. Given the small scale geographic variation in intensity of malaria transmission (Sharp & le Sueur 1996; Smith et al 1995)), parasite prevalence at each sentinel site (21 in all) was compared to post intervention prevalence. A convenience sample was taken at the predetermined sentinel sites and sample size was calculated based on a projected 20 % reduction in prevalence**,** post intervention to being statistically significant . Parasite prevalence surveys were carried out in December 1999, June 2000 and June 2001. An additional survey was carried out in KwaZulu-Natal in January 2001. All age categories were sampled, with the exception of the June 2000 and

2001 surveys in Mozambique when this was confined to the category of 2 to <15 years of age. Microscopic malaria diagnosis was by giemsa stained thick smears.

Malaria case totals for Swaziland and South Africa were available as a result of the respective, Malaria Information System's (MIS) (Sharp and le Sueur 1996, Sharp *et al* 2001). The MIS systems document malaria cases diagnosed at health facilities, and in the case of South Africa, include active case detection as well.

Window traps (Muirhead Thomson 1959) were fitted on 4-8 homes at each of the sentinel sites in Zone 1, Mozambique and mosquitoes cleared daily by the homeowner and preserved in isopropanol alcohol for later genetic species identification (Bredenkamp *et al* 1995; Koekemoer *et al* 2000).

Hudson expert pumps with 4001 nozzles were used to spray houses. Spraymen and managers were trained in spraying technique and safety measures appropriate to the insecticide and personal protection equipment used. Spraymen and managers were trained in spraying techniques, safety measures and personal protection equipment appropriate to the insecticide.

House spraying with DDT in Swaziland started in 1981 and spray dates during the study were September to December during 1999 and 2000. The application rate was $2gm^{-2}$.

House spraying with DDT in KwaZulu-Natal started in the 1950's and in 1996 policy changed to the use of a synthetic pyrethroid (Sharp et al 2001). The first round of DDT spraying, following it's reintroduction, started in February 2000, with the second round starting in October 2000. The application rate was $2gm^{-2}$.

Spraying in Mozambique with Bendiocarb at 400mg per m^2, started in October 2000 and was completed during February 2001, 45145 structures were sprayed using 926 kg's of Bendiocarb.

Chloroquine was used as first line treatment and Sulphadoxine/pyrimethamine as second line treatment in both Swaziland and Mozambique. Sulphadoxine/pyrimethamine was used as first line treatment in KwaZulu-Natal until February 2001 when Lumafantrine/artemisinine was introduced.

Statistical analysis was carried out using the statistical package Stata. For an assessment of the effect of spraying, relative risks between different years were calculated for individual sites. Similarly, relative risks were calculated to assess differences in prevalence of infection between adults and children. A combined Mantel-Haenzel weighted relative risk was calculated for all sites combined. Logistic regression was carried out to seek confirmation of associations, and to control for confounders where appropriate.

Results

Parasite Prevalence surveys

A comparison of 1155 Hrp-2 antigen malaria tests and thick bloodsmear malaria diagnosis from Mozambique sentinel sites, showed a prevalence of 67.8% based on the rapid tests and 60.5% on the bloodsmears.

Mozambique

For 1999, child as well as adult prevalence surveys were conducted at all sites. Average infection rate in the younger age category was 64 % as opposed to 30 % in the adult category. The overall relative risk of infection for children compared to adults was 2.12 (95% CI 1.87, 2.41), with no evidence of heterogeneity in relative risks between sites (p=0.90).

Since there was no evidence of any difference in intra-site prevalence in children at the 6 sites between 1999 and 2000 (p=0.82), data from these two years were combined and compared with prevalence values obtained from surveys taken in June 2001 after the first round of spraying (table 1). The average infection rate from all sites for the two baseline years was 62 % and 38% for the post intervention survey. The Mantel-Haenzel adjusted overall relative risk of infection in children <15 across all seven sites was 0.56 (95% CI 0.51, 0.61) for June 2001 compared to average risks for the two previous years combined. Six of the 7 sentinel sites in zone 1 following house spraying with Bendiocarb, showed a statistically significant reduction in infection rates and relative risk. There was, however, significant between site variation in relative risks (p<0.0001), both before and after intervention

	1999/ 2000		**2001**				
	Total	**% Prev**	**Total**	**% Prev**	**Relative Risk**	**95% Conf. Interval**	
Bela Vista	231	**82**	119	**54**	0.65	0.55	0.78
Catuane	204	**89**	120	**55**	0.62	0.52	0.73
Changalane	186	**71**	120	**29**	0.41	0.31	0.55
Namaacha	269	**31**	122	**10**	0.31	0.18	0.55
Ponto do Ouro	202	**14**	111	**22**	1.51	0.92	2.46
Salamanga	217	**83**	120	**60**	0.72	0.62	0.85
Zitundo	209	**69**	107	**33**	0.47	0.35	0.63

Table 1. Mozambique, Zone 1. Parasite prevalence rates and sample size in the category 2 to<15 years of age for the 1999 and 2000 surveys combined and for the post intervention survey of June 2001 at 7 sentinel sites .

Swaziland

There was no evidence of any raised risk of infection in children, compared to adults in the three surveys conducted (Relative Risk 1.02, 95% CI 0.67 - 1.57). Survey results for adults and children were therefore combined. Prevalence was consistently low (<10%)

and logistic regression showed that there was no evidence of between year variation (p=0.14) over the study period.

There was no significant difference in parasite prevalence rates: i. Of the 3 surveys ii. Between age categories iii. Between sentinel sites.
DDT house spraying was carried out between October 1999 and December 1999 and repeated during the same period in the 2000 season.

	1999/2000		2001	
	Total	**% Prev**	**Total**	**% Prev**
Lomahasa	343	**8**	188	**3**
Mambane	395	**2**	195	**7**
Mhlumeni	184	**3**	170	**6**
Shewulala	398	**3**	180	**1**

Table 2. Swaziland parasite prevalence rates and sample size for all ages, for the 1999 and 2000 surveys combined and for the post intervention survey of June 2001.

KwaZulu-Natal

The prevalence rates at the three sentinel sites in KwaZulu-Natal ranged from 10 to 40% in 1999 with an average parasite rate of 19% in children and 17% in adults (Table 3). Vector control in the area was by annual house spraying with a synthetic pyrethroid between 1996 and 2000. Due to pyrethroid resistance (Hargreaves *et al*., 2000), *a* National Policy decision was made in 2000 to use DDT for vector control *(delete* by house spraying*)*, with the first spray round starting in January 2000, followed by a second spray round starting in July 2000.

Comparison of parasite prevalence survey results for children and adults in KwaZulu Natal showed that children had a relative risk of 1.49 (95% CI 1.20, 1.85) compared to adults. We therefore present results for adults and for children separately. Table 4 summarises the results for all sites combined, showing comparison between years before and after the first and second round of spraying with DDT. There was a significant reduction in prevalence in adults (but not in children) after the first round of spraying, and a further significant reduction in both adults and children after the second round of DDT spraying (Tables 3 & 4). Following the second spray round with DDT, prevalence rates reduced dramatically to < 3 percent and remained low as evidenced by the following survey in June 2001 (Table 3). There was significant difference between the two sets of surveys taken after the second round of DDT spraying. There was no evidence of significant variation between sites except for the one measurement indicated in Table 4.

	Children		Adults	
Survey	**Number**	**% Prevalence**	**Number**	**% Prevalence**
Dec 99	365	19	338	17
June 2000	397	19	341	10
Feb 2001	513	3	688	2
June 2001	491	6	473	4

Table 3. Sample size and prevalence rates in children and adults during the four sampling periods.

		Adults		Children	
Survey	**Comparison year (reference)**	**Relative Risk***	**95% CI**	**Relative Risk***	**95% CI**
June 2000	Dec 1999	0.61	0.42, 0.90	1.29	0.95, 1.75
Feb 2001	Dec 1999	0.11	0.06, 0.20	0.13[§]	0.08, 0.24
Feb 2001	June 2000	0.19	0.10, 0.35	0.12	0.07, 0.21
June 2001	Feb 2001	1.97	0.98, 3.93	1.97	1.01, 3.82

* Mantel-Haenzel weighted overall relative risk

[§] Significant heterogeneity between sites (p=0.0001).

Table 4. Relative risks showing comparison of prevalence of infection between years before and after DDT spraying, for adults and for children, for prevalence surveys in KwaZulu Natal.

Malaria Incidence

The malaria case totals for Swaziland are outlined in Table 5, showing the statistically significant reduction between the 1999/2000 and the 2000/20001 malaria seasons.

June to June	Malaria Cases
1999/2000	4005
2000/2001	1395

Table 5. Confirmed malaria case totals for the 1999 to 2001 period in Swaziland.

Malaria case totals for KwaZulu-Natal are shown for the period January to June to enable reductions post house spraying with DDT to be evaluated (Table 6), a statistically significant reduction.

January to June	Malaria Cases
2000	31 974
2001	7 682

Table 6. Confirmed malaria case totals for the January to June periods of 2000 and 2001.

Discussion

Malaria control using DDT has been highly effective in Swaziland as shown by the consistently low parasite prevalence (<10 %) during the study period in comparison to the data from Mozambique prior to house spraying and KwaZulu-Natal prior to the policy change to DDT in 2000.

DDT was effectively used in vector control by house spraying in KwaZulu-Natal from 1949 to 1996 when the policy was changed to the use of synthetic pyrethroids. In KwaZulu –Natal, prevalence rates were high during December 1999 and this must largely be attributed to an ineffective insecticide in regard to the control of *An funestus*, the high failure rate (>60%) of sulphadoxine/pyrimethamine to effect parsitological cure (Bredenkamp et al 2002) and the close proximity of the sentinel sites to the uncontrolled malaria area of Zone 1 Mozambique. Malaria infected *An funestus* were found exiting pyrethroid sprayed houses in KwaZulu-Natal in December 1999, proven to be pyrethroid resistant (Hargreaves et al 2000) and the insecticide policy changed to DDT. It is assumed that *An. funestus* recolonised the Northern Kwazulu-Natal area from southern Mozambique where the study showed their numbers to be high and the pyrethroid resistant gene present (December 1999) in the population (Sharp *et al,* Manuscript in preparation). There was a significant reduction in the parasite prevalence rate of adults (17 to 10, but not in children) after the 1st spray round with DDT. The next parasite survey showed a further significant reduction in adults (10 to 2) as well as a highly significant reduction in children (19 to 3). This survey occurred after the 2nd round of DDT and the 1st application of Bendiocarb in the adjacent areas of Mozambique and both activities would thus have contributed to this reduction. Parasite prevalence in KwaZulu-Natal remained low (<10%) following the second DDT spray round, as evidenced by the June 2001 parasite prevalence survey. This reduction in prevalence must largely be ascribed to the DDT house spraying programme in the area and the Bendiocarb house spraying in the neighbouring area in Mozambique as first line treatment in KwaZulu-Natal was only officially changed in February 2001 and the parasite prevalence rates were already below 4%. Malaria incidence data support the reduction evident from the prevalence surveys and showed a 76% reduction in malaria cases for the first 6 months of 2001 in comparison to the same period in 2000. The contribution of the drug policy change from sulphadoxine/pyrimethamine to lumafantrine/artemisenine during this period, on malaria incidence, is under investigation.

Parasite prevalence rates in the 2 to<15 year old age category were high in Zone 1, Mozambique and ranged from 14% to 89 % with an average prevalence rate *of 62 %* over the 7 sentinel sites (*delete*of 62%*)* based on Hrp-2 antigen tests. The prevalence rates based on Hrp-2 antigen were slightly higher than the result based on thick blood smears. Prevalence data from 10 areas in Zone 1, collected during the 1937/38 period also showed high parasite prevalence rates with an average of 86% infection in the 1 to <15 year old age category (XXX). The house spraying programme, using Bendiocarb, that started in October 2000 was effected a statistically significant reduction in parasite prevalence at six of the 7 sentinel sites, with an overall reduction of 40 % following one spray round. This reduction compares well with those from the Brigades para Eradicacoa do Paludismo over the period 1961-1969 when all houses in Zone 1 were sprayed annually with DDT. Parasite ratios were reduced to <5% in all areas and remained so for

the duration of the campaign. In the high risk area of Catuane, bordering KwaZulu-Natal, parasitaemia's were only reduced to below 5% following the third year of this spraying campaign. There are no previous data on the use of Bendiocarb in a large scale house spraying programme in Africa. However the results are supported by those following DDT house spraying in the 1960's. Similar parasite prevalence reductions in the Pare–Tavete area (Tanzania) were obtained following house spraying with Dieldrin, (Draper and Smith 1960), both interventions also showed significant reductions in parasite prevalence after the initial spray round**.**

A study has been initiated to quantify the effect of population movement on transmission but at present only preliminary data is available from Zone 1, Mozambique. However, a high percentage of cases in Swaziland and KwaZulu-Natal are annually classified as originating in Mozambique. This study showed prevalence rates in children, before spraying, as high as 89% in areas bordering KwaZulu-Natal and Swaziland. The reduction in prevalence of this previously uncontrolled reservoir of infection, bordering on the adjacent controlled areas would with out a doubt impact on transmission in the latter areas. It is suggested that the reduction in parasite prevalence following house spraying in Mozambique, had a direct effect on reducing malaria cases and transmission in the neighbouring countries. This is indicated by the number of malaria cases recorded in Swaziland and Mpumalanga (South Africa), who made no major changes in their malaria control strategies during the study period eg no drug or insecticide changes. Swaziland which borders on Zone 1 showed a 65 % reduction in confirmed malaria cases during the 2000/2001 malaria season in comparison to the 1999/2000 season, in contrast, Mpumalanga only showed a 7% reduction in the number of cases between the two years. Mpumalanga does not border on Zone 1 and would therefore in all probability not have benefited to the same extent from the reduction in infected migrants. Parasite prevalence rates collected in the un-sprayed Boane area in Mozambique (north of and adjacent to Zone 1), towards extension of the spraying programme, showed a statistical significant reduction in parasitaemia between the pre and post spraying surveys. However this reduction cannot be solely attributed to an edge effect as an insecticide impregnated bed net project in the area by the local health authorities coincided with this study

The parasite prevalence data from Swaziland , an area with a long standing vector control programmes, showed no statistical difference in infections in the under and over 15 year age categories. The data from Mozambique, an area that had not benefited from vector control since the 1960's, showed a statistical difference at all, bar one of the sentinel sites with the overall risk of parasite infection in children being more than twice that in adults. In KwaZulu-Natal, where relatively high incidence rates were experienced in the late 1990s, there was evidence of higher prevalence of infection in children (relative risk 1.49), which is confirmed by separate analysis of age-specific incidence rates (Kleinschmidt & Sharp, Patterns in age-specific malaria incidence in a population exposed to low levels of malaria transmission intensity – *submitted*).

The re-introduction of DDT into KZN has resulted in a significant reduction in transmission. The introduction of the LSDI regional control initiative has resulted in a further significant reduction in transmission in adjacent areas under existing control.

This conclusion is supported by the facts that non-adjacent areas showed no significant change in transmission. In comparison adjacent control areas, both under long-term DDT usage (no change in control strategy) and those under recent DDT re-introduction, both showed highly significant reductions in transmission. The outcome is not unexpected as it is obvious that malaria does conform to national boundaries. However the study highlights how a regional approach to disease control can have significant downstream effects on transmission. The reduction in transmission in South Africa and Swaziland are dramatic in terms of human morbidity and treatment costs. There is little doubt that such a regional approach will indeed further (le Sueur et a 1993; Sharp & le Sueur 1996) Roll Back Malaria and result in substantial reductions in control cost of countries on the edge of distribution. This conclusion strongly supports the current strategy of financial support from adjacent countries, for control in Mozambique.

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Figure 1. Malaria Control sentinel sites in Swaziland, South Africa and Mozambique