REPORT

SECTION 1

"Gathering of Data on the Global Epidemiology of the Malaria Threat, Applied Interventions and Socio-economic Impact"

Mosquito (Anopheles gambiae). Wax model by Grace Edwards, c. 1915
This is one of nine wax models of insects of medical importance, commissioned for the Wellcome Museum of Medical Science (1914-1964).

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Graphic Credit: Wellcome Trust Medical Photographic Library

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1 ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
ADME	Adsorption, distribution, metabolism and excretion
AMANET	African Malaria Network Trust
An	*Anopheles*
ARC	Agricultural Research Council
MARA/AMRA	Mapping Malaria Risk in Africa
BioPAD	Biotechnology Partnerships and Development
BRICS	Biotechnology Regional Innovation Centres
BRTI	Biomedical Research and Training Institute
CBT	Cape Biotech Trust
CSIR	Council for Scientific and Industrial Research
CRO	Contract Research Organisations
CSIR	Council for Scientific and Industrial Research
DANIDA	Danish International Development Agency
DGIS	Directorate-General for International Co-operation
DHFR	Dihydrofolate reductase
DNDi	The Drugs for Neglected Diseases Initiative
DST	Department of Science and Technology
DTI	Department of Trade and Industry
ECoBio	East Coast Biotechnology Regional Innovation Centre
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IOWH	Institute for One World Health
IKS	Indigenous Knowledge Systems
IND	Investigational New Drug Application
IPT	Intermittent Presumptive Treatment
IRS	Indoor Residual Spraying
ITN	Insecticide treated nets
LSDI	Lubombo Spatial Development Initiative
MAG	Malaria Advisory Group
MIM	Multilateral Initiative for Malaria
MiTech	Missions in Technology
MMV	Medicines for Malaria Venture
MRC	Medical Research Council
NDA	New Drug Application
NIAID	National Institute of Allergy and Infectious Diseases
NICD	National Institute of Communicable Diseases
NIH	National Institute of Health
NRF	National Research Foundation
P	*Plasmodium*
PPP	Public Private Partnership
REDIBA	Research Development Initiative for Black Academics
RBM	Roll Back Malaria
R&D	Research and Development

RISA	Research and Innovation Support Agency
RPG	Research Project Grants
RU	Rhodes University
PPD	Product Process Development Scheme
RMCC	Regional Malaria Control Council
SANBI	South African National Biodiversity Institute
SATMERG	South African Traditional Medicines Group
SME	Small and Medium Enterprises
SP	Sulphadoxine-pyrimethamine
SPII	Support Programme for Industrial Innovation
SU	Stellenbosch University
TAP	Technology Advancement Programme
THRIP	Technology and Human Resources for Industry Programme
UCT	University of Cape Town
UNICEF	United Nations Children's Fund
UP	University of Pretoria
USAID	US Agency for International Development
Wits	University of Witwatersrand
WHO	World Health Organisation
WHO/TDR	WHO Special Programme for Research and Training in Tropical Diseases

2 EXECUTIVE SUMMARY

Malaria is the world's most important parasitic disease. It rates amongst one of the major health and developmental challenges facing many of the poorest countries in the world. At the end of 2004, 107 countries and territories had areas at risk of malaria transmission, with some 3.2 billion people, about 40% of the world's population, living in risk areas. There are estimated to be between 350 and 500 million clinical cases, and between 1 and 2 million deaths annually. Around 57% of the world's clinical malaria cases occur in Africa, 30% in Asia and around 5% in the Americas.

Of these cases 300 million were attributed to *Plasmodium falciparum,* by far the most aggressive species as it can progress to severe or complicated malaria. Nearly all malaria deaths result from *P. falciparum*. This species is distributed globally but is especially common in Africa, with over 70% of the world's cases. It is estimated that at least one million people die in Africa from malaria each year, with most of these deaths occurring south of the Sahara. The disease is the principal cause of death of at least one fifth of all young child deaths in Africa. It is estimated that 3,000 children under the age of five years fall victim to malaria each day. Malaria also contributes indirectly to many additional deaths, mainly in young children, through synergy with other infections and illnesses. Malaria is second only to AIDS in the list of the continent's list of killer diseases.

The estimated clinical cases of *P. falciparum* malaria annually in the South African Malaria Control region is in the order of 39 million. The SAMC, set up in 1997 by the WHO to fight malaria in Southern Africa, includes Angola, Botswana, Malawi, Mozambique, Namibia, South Africa, Swaziland, Tanzania and Zimbabwe. Out of the 131 million people living in the SAMC area, approximately 61% live in malarious areas. In the predominantly stable transmission countries there are an estimated 12.1 million under-five year olds and 2.9 million pregnant women at risk of severe malaria. In the unstable transmission countries all people living in malarious regions are at risk of malaria it is estimated that there are 12.4 million people at risk.

The disease takes an economic toll as well because of reduced productivity. Within Southern Africa the burden of malaria is greatest within poor communities located in malarious areas. Such communities are resource-poor, have limited access to health and other social services, and low levels of literacy. Communities with low incomes, limited education and poor access to health care are least able to engage in malaria control activities. In poor households, the costs of malaria prevention are estimated to be as high as 20% of the annual income. Malaria illness can cause to absenteeism from work and school, poor scholastic performance, lack of labour for cultivation, and a decline in child care; malaria deaths can lead to funeral costs, loss of an income-earner and a rise in orphanhood. In endemic African countries, malaria accounts for 25–35% of all outpatient visits, 20–45% of hospital admissions and 15–35% of hospital deaths.

Ultimately, malaria has a burden on Sub-Saharan Africa's economic performance. The combined impact of the above factors, will negatively affect the gross domestic product and socio-economic development is delayed. The burden of malaria is estimated to be responsible for an average loss of 1.3% of economic growth annually in countries with intense transmission. UNICEF states that malaria costs Africa between US$ 10 – 12 billion annually in lost gross domestic product.

During the 20th century, malaria had effectively been eliminated or effectively suppressed in many parts of the world but is now undergoing a resurgence. Despite global economic development, the mortality rate for malaria is higher than 30 years ago. It is returning to areas from which it was eradicated as well as spreading to new areas such as Central Asia and Eastern Europe. In some areas such as sub-Saharan Africa, malaria transmission

continues at high intensity. Factors that have been recognised as contributing to this increase include the state of socio-economic decline and increasing poverty in the most malarious regions resulting in a breakdown of control programmes and the general collapse of local primary health care services, coupled with the growing resistance of parasites to commonly used antimalarial drugs and increasing resistance of mosquito vectors to insecticides.

Recognizing that there are proven and effective interventions against malaria, the Roll Back Malaria (RBM) programme was introduced in 1998 by the World Health Organisation (WHO), UNICEF, NHDP and the World Bank with the goal of halving the global burden of malaria by 2010. The partnership includes malaria-endemic countries, their bilateral and multilateral development partners, the private sector, academia and international organizations. The Abuja declaration in 2000 committed 44 African countries to halve the malaria mortality in Africa by 2010. The following core technical strategies for the sustainable control of malaria have been identified:

- Improved and prompt treatment of clinical attacks of malaria with an effective drug
- Increased use of insecticide treated bed nets and other materials (ITN) and other locally appropriate means of vector control;
- Improved prevention and treatment of malaria in pregnant women in highly endemic areas.

Most countries however did not start implementing the programmes to provide the tools and strategies recommended by RBM until 2000. In many countries in Africa where the burden of malaria is greatest, scaling up access to treatment and prevention began even more recently. Some countries in Africa have reached or exceeded at least some of these targets with recent increases in funding.

On average half of African children with fever are treated with an antimalarial drug, mostly involving chloroquine, against which resistance of the *P. falciparum* parasite is very high. Faced with this increasing resistance to monotherapy, the WHO has recommended a change to artemisinin-based combination therapy (ACT). Artemisinin and its derivatives Artesunate and Artemether are a new class of antimicrobial drug with potent activity against *P. falciparum*. They show efficacy in both severe and uncomplicated malaria. By the end of 2004, 23 African countries had adopted ACTs in their national drug policy.

The number of insecticide treated nets (ITNs) distributed has increased dramatically during the past 3 years in more than 14 African countries. Subsidized or free-of-charge ITN distribution, often linked to antenatal care and/or child immunization services, has proved increased coverage of the most vulnerable populations. In most African countries, many more households however have mosquito nets not treated with insecticide. Scaling up of insecticide re-treatment services will therefore also be an important factor in increasing ITN coverage. Efforts to prevent burden of asymptomatic infections in pregnant women residing in areas of stable malaria transmission have been increased through partnerships between malaria and reproductive health programmes. A number of African countries, in addition to scaling up delivery of ITNs to pregnant women, are now in the process of implementing IPT for pregnant women.

It is estimated that the annual cost to provide the minimal set of malaria interventions required to effectively control malaria is in the order of US$ 3.2 billion per year. Of this, US$ 1.9 billion is required for Africa alone. Whilst financial support and commitment to malaria control have increased since the inception of RBM there remains a huge resource gap, especially in high-burden countries which are typically the poorest countries. Sustained and increased donor assistance is hence required for the foreseeable future. In 2003, the Global Fund to Fight AIDS, TB and Malaria (GFATM) disbursed more than US$ 200 million to 28 African, 15 Asian and 4 American countries. The commitment for 2005/06 is US$ 881 million.

In South Africa, approximately 95% of malaria infections are due to the parasite, *Plasmodium falciparum*. Malaria transmission is seasonal, correlating with the rainy summer season resulting in a distinct pattern of transmission. Current high risk areas are all border areas, hence indicating the importance of a regional malaria control strategy. The malarious regions are the eastern parts of Limpopo and Mpumalanga provinces, and the north-eastern parts of KwaZulu Natal. Occasionally, small outbreaks occur in the Northern Cape and North Western Provinces.

In the 1990's the number of malaria infections in South Africa increased dramatically. Most of this increase was due to the northern KwaZulu Natal province where it borders with Southern Mozambique. These increases were attributed to climatic conditions, parasite resistance, and vector resistance. Studies by the South African National Institute of Communicable Diseases in 1999 showed that populations of the vector *A. funestus* in Southern Mozambique had developed resistance to pyrethroids. This necessitated a change to the use of DDT as an insecticide. The use of DDT has resulted in the eradication of *An. Funestus* (a potent transmitter of Malaria).

In 2001, community based drug efficacy studies in KwaZulu Natal, Limpopo and Mpumulanga showed parasitological resistance levels to sulphadoxine-pyrimethamine (SP) at varying levels. The drug policy in the three provinces was therefore changed to a fixed dose ACT therapy.

South Africa is collaborating with neighbouring countries, Swaziland and Mozambique, within the framework of the Lubombo Spatial Development Initiative (LSDI), a Public Private Partnership (PPP), implemented in 2000. This project involves governments, business sector and communities. The geographic region targeted by this initiative is defined as eastern Swaziland, southern Mozambique and North Eastern KwaZulu Natal, regions linked by the Lubombo Mountains. The programme is run by the Regional Malaria Control Commission (RMCC). Baseline surveys conducted by the RMCC in 1999 revealed that there was a marked difference in prevalence rates between the three countries. The objective over 5 years is to reduce the prevalence of *P. falciparum* in Maputo province, South Africa and Swaziland. The LSDI has already achieved malaria incident reductions of 96% in KZN, 91% in Swaziland, and 86% in participating areas of Mozambique. This has been shown to have a positive impact on socio-economic development in the region.

Subsequent to the dramatic increase in malaria cases and deaths in the late 1990's, robust malaria interventions and mobilisation of additional resources have ensured that malaria cases and deaths have again declined. The reduction in malaria cases and deaths since 2000 can be attributed to a number of interventions such the change of first-line treatment to co-artemether, the re-introduction of DDT spraying, as well as the regional approach to malaria control in the LSDI. The LSDI now protects approximately 4.7 million people in 1.8 million houses over an area of 100,000 km^2. Parasite prevalence in children between the ages of 2 and 15 was between 60 – 70% when the programme started, it is now less than 5%.

The South African Malaria Control Programme has clearly managed through the various intervention programmes to decrease the incidence of malaria annually and to restrict malaria to back to the areas bordering neighbouring countries. The resultant control has been followed by significant economic development, in some cases opening up previously uninhabitable areas for agriculture, mining and industry. Strategies to address cross border malaria control between the Limpopo area and Mozambique are expected to have a similar impact on malaria reduction in South Africa as the achievements of the LSDI malaria initiative.

The challenge in South Africa in the long-term is to maintain this trend. A recent South African Health Systems Trust review states some of the challenges facing the malaria programmes in South Africa. These include increasing population movement across borders as South Africa's economy grows. As a result, continued

parasite and vector transmission is viewed as highly likely. The monitoring of vector resistance to insecticides is critical to prevent future epidemics. Similarly, the monitoring of drug resistance is also vital in light of the rapid development of parasite drug resistance recently experienced in South Africa. Furthermore, as the type of housing structures in rural areas changes from mud huts to western style, coupled with increasing insecticide resistance levels in malarious regions, alternative insecticides and/or alternative vector interventions will be required. With these new challenges, the Health Systems Trust concludes that the malaria programmes will need to strengthen the range of interventions available at district level. Alternative vector control methods may be necessary, based on sound, scientific evidence.

The focus of malaria control programmes globally is on the provision of effective and affordable interventions and the management of infected children through early treatment with effective antimalarial drugs. The number of effective drugs to treat malaria is small, and growing resistance to these drugs is a significant threat to control of the disease. Most of the antimalarial drugs used today were developed over 30 years ago, and there has been very little interest by the pharmaceutical industry in developing new products. Combination artemisinin therapies have been shown to be the most effective antimalarial treatment available at present. Their production is lengthy and relatively costly and whilst the drug is sold to the public sector at cost, it is still significantly more expensive than traditional first-line drugs. The development of cheaper ACTs is therefore a priority. Furthermore, control strategies based on early treatment require a continual search for new drugs before the *Plasmodium* malaria parasites develop resistance. The long-term strategy should therefore be to interrupt the transmission of the parasite.

Insecticide resistance is still a major problem facing control programmes in most countries and residual house spraying is compromised by the fact that choice of alternative insecticides to DDT is limited. The use of ITNs in many areas has been implemented with variable rates of success as community take-up is often disappointing. There is therefore potential for research into improving the effectiveness of control methods through the development of insecticide-fabric combinations, as well as on technology to permanently impregnate the nets.

The lack of microscopic diagnosis in most developing countries, and the reliance on clinical symptoms for diagnosis, is contributing to the increase in the growth of resistance, increased mortality, prolonged morbidity and delayed response to emerging epidemics. Dipstick tests and other rapid, user-friendly diagnostic tests that are sensitive and specific for those areas that do not have access to laboratory apparatus are essential for meeting these challenges.

The completed genomes of *Plasmodium falciparum* and its vector *Anopheles gambiae* therefore open up new approaches to the development of drugs, vaccines, insecticides and insect repellents, as well as intervention into malaria transmission. Genetic tools will also allow the sampling of parasite, mosquito, and human genomes in malaria affected areas to support the malaria control activities. The combination of these tools is therefore essential in the battle to halt transmission of malaria in Africa and other endemic areas of the world.

3 EPIDEMIOLOGY/DISEASE BURDEN

At the end of 2004, 107 countries and territories had areas at risk of malaria transmission, with some 3.2 billion people living in risk areas. There are estimated to be between 300 and 500 million clinical cases, and between 1 and 2 million deaths annually. It is estimated that at least one million people die in Africa from malaria each year. Most of these deaths occur south of the Sahara.[1] The disease is the principal cause of death of at least one fifth of all young child deaths in Africa. [2] It is estimated that 3,000 children under the age of five years fall victim to malaria each day.

Plasmodium falciparum is by far the most aggressive species as it can progress to severe or complicated malaria characterised by multiple vital organ dysfunction. *Plasmodium vivax*, which appears widely throughout Asia, Africa, the Middle East, Oceania and South America can cause recurring and debilitating infections but rarely kills. It does however cause low birthweight, a major cause of infant mortality. Nearly all malaria deaths hence result from *P. falciparum*.

During the 20th century, efforts to control malaria combined with improved access to treatment and general socio-economic development have markedly reduced or eliminated the spread of malaria in many regions in the world. Malaria had effectively been eliminated or effectively suppressed in many parts of the world. The disease is however now experiencing resurgence. It is returning to areas from which it was eradicated as well as spreading to new areas such as Central Asia and Eastern Europe. In some areas however, such as sub-Saharan Africa, malaria transmission continues at high intensity. Factors that have been recognised as contributing to this increase include:

1. Resistance of parasites to commonly used antimalarial drugs
2. Breakdown of control programmes
3. Various complex emergencies such as war
4. Collapse of local primary health care services
5. Resistance of mosquito vectors to insecticides

Recognizing that there are proven and effective interventions against malaria, the Roll Back Malaria (RBM) programme was introduced in 1998 by the World Health Organisation (WHO), UNICEF, NHDP and the World Bank with the goal of halving the global burden of malaria by 2010. The partnership includes malaria-endemic countries, their bilateral and multilateral development partners, the private sector, academia and international organizations. The Millennium Development goals for malaria are to have halted the disease and begun to reverse the incidence of malaria by 2015. The Abuja declaration in 2000 committed 44 African countries to halve the malaria mortality in Africa by 2010. The following core technical strategies for the sustainable control of malaria have been identified:

- Improved and prompt treatment of clinical attacks of malaria with an effective drug;
- Increased use of insecticide treated bed nets and other materials (ITN) and other locally appropriate means of vector control;
- Improved prevention and treatment of malaria in pregnant women in highly endemic areas.

A general problem in the determination of the impact of malaria and the definition of populations at risk and therefore the ongoing monitoring of programmes such as the RBM, is the lack of data on incidence and disease burden, especially in the most affected areas. Estimates in many areas, are based on official and reported figures and might be underestimated significantly. The Roll Back Malaria Monitoring and Evaluation Reference Group (MERG) task force on malaria morbidity devised an improved method for estimating the incidence of clinical malaria episodes. This study estimated a global total for clinical malaria of 401 million cases in 2004 (range 350 –

500 million). Of these cases 290 million (range 270 – 400 million) were attributed to *P. falciparum*.[3] These estimates are proposed for use in tracking trends and progress of the RBM's objectives and the Millennium Development Goals.

Provisional country-level estimates in the RBM study of the rates of total clinical incidence of malaria show that around 57% of the world's clinical malaria cases occur in Africa, 30% in Asia and around 5% in the Americas. For *falciparum* malaria, the estimated regional distribution is around 72% in Africa and 19% in Asia. These numbers are about 6-fold higher than cases reported globally and 17-fold higher in non-African countries by the national health systems due to for example the weak system of reporting in some regions.

Table 1: RBM MERG Study Country Level Estimates 2004

Region	Total Clinical Cases		% Falciparum	Falciparum Cases	
Africa	228,807,268	57%	93%	212,790,759	73%
Middle East	23,399,073	6%	46%	10,878,229	4%
Europe	717,714	0%	0.30%	2,153	0%
South America	11,858,384	3%	18%	2,192,615	1%
South East Asia	121,206,667	30%	49%	59,391,267	20%
Western Pacific	15,194,631	4%	32%	4,936,736	2%
	401,183,737	**100%**		**290,191,759**	**100%**

The attached maps Appendices 1, 2 and 3, from the 2005 World Malaria Report shows the estimated incidence of clinical malaria episodes by any species, as well as the estimated incidence of *P. falciparum* episodes. Both maps represent incidences as country level averages.

Another study published recently in Nature[4] by Snow et al, provided estimates of the global distribution of *P. falciparum*. Using a combination of geographic, epidemiological and demographic data, they estimated that there were 515 (range 300 – 660) million episodes of clinical *P. falciparum* malaria in 2002. This estimate is 200% higher for areas outside of Africa than previous WHO reports, again indicating the previous reliance upon passive reporting. The contribution of Africa is 70%, and 26% for Asia.

A summary of the burden of malaria by region follows below.

3.1 ASIA[5]

In 2004, it was estimated that over 40% of the population in this sub region is at risk of malaria. The majority of malaria cases are due to the *vivax* parasite (75%). The estimated contribution to the global burden of clinical *falciparum* malaria cases is 25%. South East Asia for example has the highest rate of drug resistance in the world. Multi-drug resistance has contributed to the re-emergence of malaria in many areas. In lights of this, many countries have adopted various control strategies, including vector control for selected areas and Insecticide Treated Nets (ITN) distribution in all endemic countries. All countries in this region use Indoor Residual Spraying (IRS) and/or larviciding for vector control. Epidemic preparedness and surveillance are key control strategies in all affected countries. A number of countries in this region have reported substantial successes with reduced malaria incidence levels.

Malaria remains a significant problem in the eastern Mediterranean sub- region. In some areas, over the past 30 years, health systems have been destroyed due to various emergencies resulting in an aggravation of the disease situation. The most serious problems being in Afghanistan and Yemen where up to 60% of the population may be at risk of *P. falciparum*. Countries with low to moderate levels of endemicity are the Islamic Republic of Iran and Saudi Arabia. Oman and Syria have residual malaria transmission and imported cases. However, high rates of population movements complicate the control of malaria in border areas of countries such as Iraq, Syria and Turkey.

Vivax malaria has resurged in Central Asia and Transcaucasia since the early 1990s. The resurgence was aggravated by political and socio-economic situation, population migration, and a nearly complete breakdown in malaria control and prevention activities. As a result, epidemics of both large and small scale occurred in various countries in this region. Endemic *falciparum* malaria has returned to Tajikistan. RBM therefore scaled up interventions with sustained efforts keeping malaria under control, but with incidence rates 10-fold higher than in 1990.

In the Western Pacific region, malaria control was revitalised in the mid-1990s following resurgence in the disease due to economic decline, population movements and breakdown of disease control and health care services. Rates of reported cases have thus fallen between 1992 and 2003. Key strategies include vector control through the use of ITNs and IRS, epidemic preparedness and prompt and effective treatment.

3.2 THE AMERICAS

Malaria transmission occurs in 9 countries in the Amazon rainforest and 8 countries in Central America and the Caribbean, with an estimated 14% of the population being at risk. The number of cases in the region has remained fairly stable since 1990, with a slight decrease due to a reduction in cases in Mexico, and other countries in Central America. Isolated epidemics have resulted from population movements associated with mining and forestry work. Overall, 92% of the malaria cases are due to the *vivax* parasite. In South America, 25% of reported cases are due to P. *falciparum*, the remainder being *P. vivax*. In Central America and the Caribbean, around 10% of cases are caused by *P. falciparum*. The region contributes 1% to the global burden of clinical *falciparum* malaria.

All of these countries use IRS and/or larviciding in their control strategies, with 9 countries including the use of ITNs. The majority of the Amazon countries have recently changed national drug policies to use artemisinin-based drugs in the treatment of *falciparum* malaria due to the emergence of chloroquine resistance. In Central America north of the Panama Canal, chloroquine is still effective for treatment and prophylaxis and *falciparum* malaria as well as for the treatment of *vivax* malaria throughout the region.

3.3 AFRICA

Africa remains the region with the rates burden of malaria cases and deaths in the world. In 2000, malaria was the cause of death of around 20% of children under the age of 5. During the 1980s and 1990s the burden of malaria increased in Africa, primarily due to resistance to commonly used antimalarial drugs, deterioration of primary health services in many areas, and the emerging resistance of mosquitoes to insecticides used for vector control. Maternal anaemia in pregnancy, low birth weight and premature delivery are estimated to cause 75,000 – 200,000 infant deaths in Africa south of the Sahara.[6] Epidemics can result in up to 12 million additional malaria episodes per annum.[7]

The majority of the burden in Africa results from the countries south of the Sahara. The attached Mapping Malaria Risk in Africa (MARA/AMRA) maps, Appendices 3 and 4) indicates the distribution of endemic malaria in

Africa and in South Africa. In contrast, malaria in the five northern most African countries has been well controlled or eliminated. Northern African countries such as Egypt and Morocco have only residual transmission and imported cases. In this region, the disease was caused mostly by *Plasmodium vivax*, and transmitted by mosquitoes easier to control than those in Africa south of the Sahara. Surveillance continues in this region to ensure that a reintroduction of malaria parasites to local mosquito populations and the introduction of other more efficient malaria mosquito species does not occur.

Most people at risk of malaria in Southern Africa live in areas of stable transmission. Africa south of the Sahara includes malaria-free areas, as well as unstable and stable transmission areas. Countries with predominantly stable transmission are Angola, Malawi, Mozambique, Tanzania and Zambia. Within these countries however there are areas with unstable transmission that have a high risk of epidemics. The unstable areas are prone to epidemics as the risk of malaria is more seasonal and less predictable. Unstable areas include: Botswana, Namibia, South Africa, Swaziland and Zimbabwe. Lesotho, Mauritius and Seychelles do not have locally acquired malaria, all cases are imported.

Few countries in Africa south of the Sahara report malaria case rates each year. [8] Case rates reported hence represent only a fraction of the actual malaria burden in the region. In addition, whereas most countries in North Africa, all reported cased are confirmed by laboratory diagnosis, usually microscopy, in sub-Saharan Africa, most cases are diagnosed and reported based on purely clinical grounds without laboratory testing.

In Africa, most of the cases were estimated to occur in Nigeria, DRC, Tanzania, Uganda and Ethiopia. Based on the RBM MERG Study, the estimated clinical cases of *P. falciparum* malaria annually in the South African Malaria Control region is in the order of 36 million. The SAMC was set up in 1997 by the WHO to fight malaria in Southern Africa. Countries include: Angola, Botswana, Malawi, Mozambique, Namibia, South Africa, Swaziland, Tanzania and Zimbabwe.

Table 2: RBM MERG Study Africa Estimates 2004

	Clinical Cases	P. Falciparum Cases
North	1,880	1,748
Central	41,312,061	38,420,217
East	38,602,190	35,900,037
West	110,125,398	102,416,620
South/SAMC	38,765,739	36,052,137
	228,807,268	**212,790,759**

Out of the 131 million people living in the SAMC area, approximately 61% live in malarious areas. There are an estimated 14.0 million under-five year olds and 3.3 million pregnant women at risk of severe malaria. In the unstable transmission countries (Botswana, Namibia, South Africa, Swaziland and Zimbabwe) where all people living in malarious regions are at risk of malaria it is estimated that there are 12.4 million people at risk. The table below indicates the population at risk in the SAMC area.[9]

Table 3: SAMC Population at Risk

Country	Total Population	Population in malarious regions (%)	No. of people in malarious regions	No of under 5 at risk	No. of pregnant women
Angola	11,967,000	100%	11,967,000	2,297,000	568,000
Botswana	1,551,000	40%	620,400	97,200	21,600
Malawi	10,377,000	100%	10,377,000	1,933,000	493,300
Mozambique	16,118,000	100%	16,118,00	2,836,000	682,000
Namibia	1,653,000	66%	1,090,980	172,260	38,940
South Africa	44,295,000	10%	4,429,500	594,300	131,100
Swaziland	931,000	30%	279,300	45,000	10,200
Tanzania	32,189,000	90%	28,970,100	5,085,000	1,191,600
Zimbabwe	11,924,000	50%	5,962,000	987,500	219,000
TOTAL	**131,005,000**		**79,814,280**	**14,047,260**	**3,355,440**

3.4 SOUTH AFRICA

A committee called the Malaria Advisory Group (MAG) consisting of national, provincial malaria officers, parastatal offers and malaria experts from the public and private sector was appointed in 1994. MAG is instrumental in the formation of the malaria control policy and continues to review the control programme giving particular attention to challenges when they arise. The latter have included changes in insecticide and drug policy in response to the increase in resistance.

South Africa has a national malaria control policy's goals and strategies are in keeping with the WHO Global Malaria Control strategy as well as its 2001 – 2005 Health Goals, Objectives and Indicators. At the national level, the key indicators for monitoring malaria control include: Malaria cases, malaria deaths, and malaria case fatality rates. Monthly data is collected at the national level. South Africa is also a signatory to the Ajuba Declaration in committing itself to the Malaria Rollback Programme (RBM. Malaria is a notifiable disease in South Africa, as it is a life threatening disease and epidemic in nature. A vigilant malaria surveillance programme exists in malaria affected areas, however in the private sector and non-malarious areas, malaria notification is not optimal.

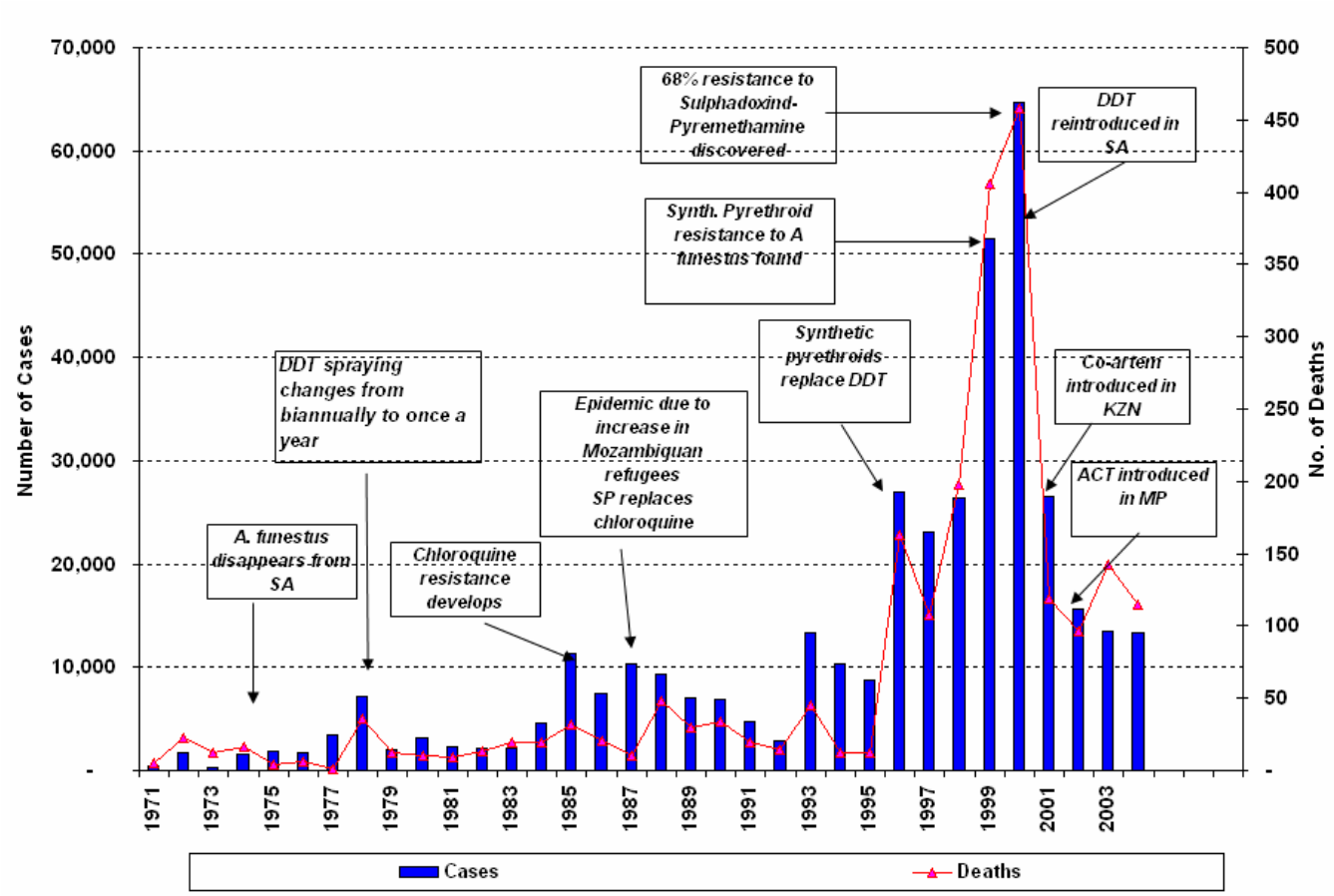
In South Africa, approximately 95% of malaria infections are due to the parasite, *Plasmodium falciparum*. Malaria transmission is seasonal, with cases starting to rise in October, peaking in January to February, and waning thereafter. Malaria case peaks correlate with the rainy summer season resulting in a distinct pattern of transmission. The disease in South Africa in the late 1930s before malaria control was introduced, was characterised by inter-annual variation with severe epidemics as far south as Durban, and reaching Pretoria. Current high risk areas are all border areas, hence indicating the importance of a regional malaria control strategy.[10] The malarious regions are the eastern parts of Limpopo and Mpumalanga provinces, and the north-eastern parts of KwaZulu Natal. Occasionally, small outbreaks occur in the Northern Cape and North Western Provinces. An official malaria transmission map is produced by the Medical Research Council after consultation with the MAG. The low, intermediate and high risk zones are determined using malaria notification data. It is updated every two years.

Between 1996 and 2000, the number of malaria infections increased dramatically. Most of this increase was due to the northern KwaZulu Natal provinces where it borders with Southern Mozambique. (See Figure 1 below) These increases were attributed to climatic conditions, parasite resistance, and vector resistance. Studies by the South African National Institute of Communicable Diseases showed that populations of the vector *A. funestus* in

Southern Mozambique had developed resistance to pyrethroids. [11] Four years after South Africa had ceased spraying with DDT, the country experienced the worst malaria epidemic since the introduction of house spraying in the 1950's.

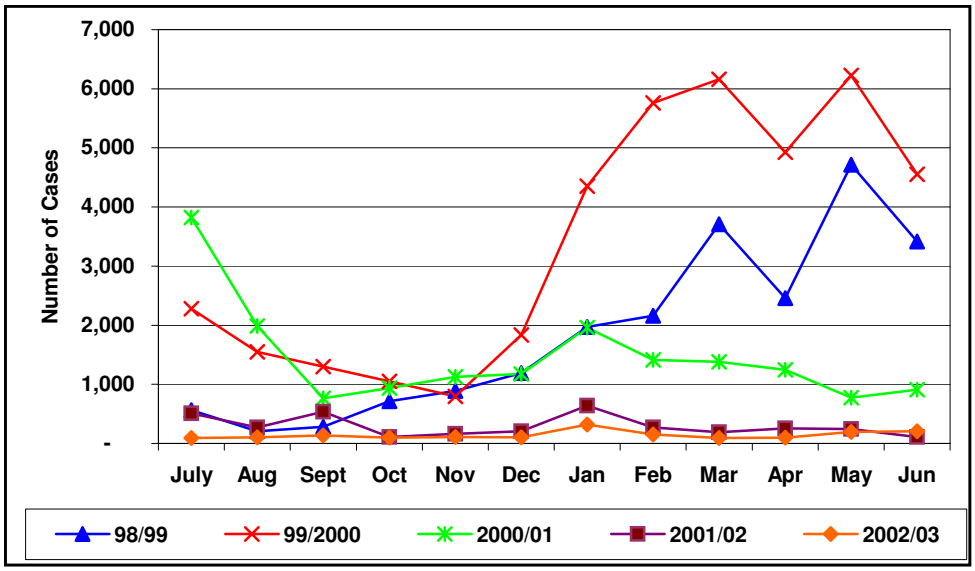
Subsequent to this dramatic increase, robust malaria interventions and mobilisation of additional resources, malaria cases and deaths have again declined. All traditional housed in the high risk area were sprayed with DDT in March – May 2000 and again in October – November 2000. Malaria incidence in the KZN area dropped dramatically during the 2000/2001 summer. Overall, the malaria cases decreased by 41% when compared to 2001.

Figure 1: Annual Notified Malaria Cases and Deaths in South Africa[12]



The graph below depicts the reported malaria cases seasonally in South Africa over the past 5 malaria seasons. The epidemic in the late 1990s can clearly be seen, as can the reduction of cases subsequently.

Figure 2: Reported Malaria Cases by Season in South Africa 1999 - 2003



The provincial malaria situation is outlined in table 4 below.

Table 4: Annual reported cases of malaria by province 1999 – 2003 (calendar years)[13]

	KZN	LP	MP	Rest of SA	Total
1999	27,238	11,228	11,741	1,237	51,444
2000	41,786	9,487	12,390	959	64,622
2001	9,473	7,197	9,061	775	26,506
2002	2,345	4,836	7,965	503	15,649
2003	2,042	7,010	4,335	72	13,459
2004	4,417	4,888	4,064	19	13,388

In Limpopo, an outbreak of malaria occurred in January 2003 in the North-eastern parts of the province, representing a 49% increase in the number of malaria cases in comparison to the same period in 2002. However, following the 2000/1 epidemic season, reported malaria cases in successive seasons have declined. In Mpumalanga, following the 2000/1 epidemic season, reported malaria cases have decreased, with a 53% decrease in the number of reported cases for 2002/03 in comparison to the 2001/02 season.

In comparing data from the 2001/02 season with 2002/03, the burden of malaria in South Africa appears to have shifted slightly from Mpumalanga to the Limpopo province. Limpopo accounted for 47% of all cases in 2002/03 in comparison to 32% in 2002/03. This corresponds to an increase of 15%. Overall however, the actual number of malaria cases in South Africa and in all provinces decreased over this period.

Figure 3: Proportion of Malaria cases by Province: 2001/02 season

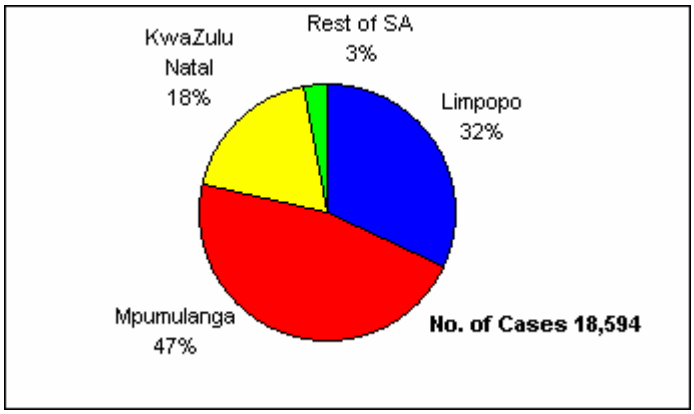
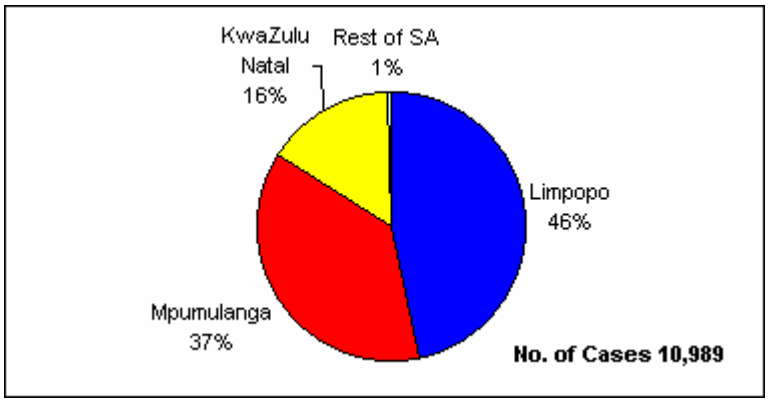


Figure 4: Proportion of Malaria cases by Province: 2002/03 season



The reduction in malaria cases and deaths since 2000[14] can be attributed to a number of interventions such as:

- The introduction of effective combination therapy (Co-artem®, artemether plus lumefantrine)
- Insecticide policy changes to DDT
- The regional approach to malaria control between South Africa, Mozambique and Swaziland, and the extension of vector control to southern Mozambique, which is believed to have had a major influence on malaria incidence in the Lubombo corridor.

4 CONTROL of MALARIA– DISEASE INTERVENTIONS

4.1 INTRODUCTION

After World War II, a global campaign to eradicate malaria began. DDT was sprayed widely, coupled with the coating and draining of breeding grounds. This resulted in the eradication of malaria in Europe, Russia and parts of Asia from 1940 to the late 1960s. There was a substantial reduction in mosquito populations and malaria morbidity in the subtropics. Controlling malaria in the tropics was however not as successful. The success of this control was hampered by a number of factors: difficult access to health facilities, deterioration of health infrastructure, and gradual resistance to insecticides. In the late 1960s, malaria eradication plans through the eradication of vectors were largely abandoned.

Malaria prevention methods have hence shifted towards local protection methods, focussing more on the partial control of breeding grounds, and on the use of insecticide-protected mosquito bed nets.[15] There are basically three tools available to curb malaria deaths, treated bed nets, insecticides, and the use of combination treatment based on artemisinin. The choice of malaria control strategies varies according to malaria endemicity. The table below shows the priority malaria control strategies in Africa by epidemiological setting. These strategies generally conform to the key strategies advocated by the Roll Back Malaria programme.[16]

Table 5: Priority malaria control programmes

Epidemiological Setting	Control Strategy
Stable Endemic Large parts of East, Central and West Africa	**Prevention:** - ITN for children under 5, pregnant women and people living with HIV/AIDS - Intermittent Presumptive Treatment (IPT) in pregnancy - *IRS where appropriate* **Treatment:** - Early and effective case management (Presumptive treatment for suspected cases)
Unstable malaria: Parts of Southern Africa	**Prevention:** - IRS - Larviciding - Environmental management - ITNs **Treatment** - Early and effective case management (Presumptive treatment for suspected cases) - Diagnostics to confirm, if possible before treatment
Free of Malaria: Parts of Southern and Northern Africa.	**Prevention:** - Chemoprophylaxis and personal protective measures for travellers **Treatment:** - Early and effective case management (Presumptive treatment for suspected cases) - Diagnostics to confirm, if possible before treatment

The estimated cost of providing the minimum set of malaria interventions required to achieve the 2010 Ajuba targets and Millennium Development Goals for malaria by 2015 for the 82 highest burden countries is around $ 3.2 billion annually. According to the UN Millennium Project Task Force on Malaria that is equivalent to 2 – 3 days of US and EU farm subsidies. The estimate for Africa alone is US$ 1.9 billion. [17] Only a fraction of this is available, with the resource gap in high-burden countries being particularly wide. Governments in malaria areas provide the bulk of the funding for national malaria control programmes, for example in Africa in the period 2002/03 governments provided 71% of the funding. Nevertheless, the poorest countries, which have the highest malaria burden cannot fill the gap, and as a result donor assistance is required. In 2003, the Global Fund to Fight AIDS, TB and Malaria disbursed more than US$ 200 million to 28 African, 15 Asian and 4 American countries. The commitment for 2005/06 is US$ 881 million.

4.2 KEY ISSUES IN THE CONTROL OF MALARIA

One of the issues in the malaria vector control is the emergence of drug-resistant strains of *P. falciparum*. In the late 1950s strains of *P. falciparum* resistant to chloroquine emerged in Southeast Asia and South America. By the 1980s chloroquine resistance had spread to East Africa. Chloroquine resistance was substantiated in Kenya and Tanzania in 1978. During the 1980s chloroquine resistance had spread to all malarious areas of sub-Saharan Africa. [18] Few areas of the world have fully chloroquine-sensitive *P. falciparum* and some strains of *P. falciparum* have developed resistance to all available drugs with the exception of the artemisinin derivatives. This situation is particularly serious in Africa, where chloroquine is still the first-line treatment throughout most of the continent.

Insecticide treated bed nets, promoted widely in Africa, have been shown to reduce bites from infected mosquitoes by up to 90%.[19] Their effectiveness is however already threatened due to the emergence of pyrethroid resistance in *Anopheles funestus* in Mozambique and *An. gambiae* in agricultural areas of West Africa.[20] The implications of this resistance are far-reaching and of major concern to malaria control programmes in southern Africa. Although DDT is still 100% effective against *An. funestus*, environmental and other concerns limit its use. The effect of resistant *An. funestus* on all aspects of malaria vector control and the role of agrochemicals in the development of resistance is still unknown.[21]

4.3 PROGRESS in AFRICA[22]

In 2000 African Heads of State committed themselves to the Roll Back Malaria Initiative by halving the burden of malaria by 2010. Targets were set for specific intervention strategies at the Abuja Malaria Summit. By 2005, there should be a 60% coverage of all at-risk populations with suitable curative and preventative measures.

It is believed by many charities, including the WHO RBM, that few countries are likely to reach this target for coverage of access to prompt and effective treatment for Insecticide Treated Nets (ITN) and Intermittent Presumptive Therapy (IPT) for protection of pregnant women by 2005. Until recently, control efforts have remained too fragmented and international investment received too late.

4.3.1 <u>Access to prompt and effective treatment</u>

Surveys have now indicated that with respect to prompt and effective treatment - on average 50% of African children with fever receive access to an antimalarial drug. Most of these are however chloroquine based, the least expensive drug, against which resistance against *P. falciparum* is high. In Southern Africa, parasite resistance to chloroquine ranges between 12 – 56% with resistance against the most affordable alternative drug, sulphadoxine-pyrimethamine, reaching up to 15%.

Faced with this increasing resistance to monotherapy, the WHO has recommended a change to artemisinin-based combination therapy (ACT). Artemisinin and its derivatives Artesunate and Artemether are a new class of antimicrobial drug with potent activity against *P. falciparum*.[23] They show efficacy in both severe and uncomplicated malaria. The short half-lives of the semi-synthetic derivatives and the dihyroartesmisinin metabolite necessitate treatment over 5 – 7 days when they are used alone. Increasing they are used in combination with longer half-life drugs to reduce treatment time, and increase individual compliance.[24] The rapid clearance of the parasites by artemisinin derivatives is anticipated to reduce the changes of resistance developing to partner drugs.[25]

In the treatment of uncomplicated malaria, the artemisinin drug is used in combination with a long acting antimalarial. In severe malaria, parenteral artemether has been shown to be at least as effective as quinine and is simpler to use. Rectal preparations of artesunate and artemisinin at the rural health facilities facilitate early initiation of treatment and may reduce the proportion of patients succumbing to severe disease. All the drugs have comparable efficacy, and the choice is based upon availability, cost and quality of preparation. They are well tolerated in adults and children with no evidence to date of serious clinical toxicity.

By the end of 2004, 23 African countries had adopted ACTs in their national drug policies. Namibia, Zambia, Tanzania, and South Africa have all adopted ACTs. Angola is still conducting studies. Zimbabwe still treats malaria on a combination of chloroquine and SP as first line and oral quinine as second line. The government reports that it plans to change to ACTs in the long run. [26]

ACT treatment is however expensive, costing up to 20 times more than existing therapies, at around US$ 2 for an adult dose. Demand is estimated to reach between 130 – 220 million adult treatments in 2005.[27] In following years, at the current cost US$ 1 billion per annum would be required to provide for 60% of the affected population. In 2000, international aid for the control of malaria was only $100 million. This has increased due to the creation of the Global Fund, but is viewed as still being inadequate. Some donors such as USAID spend nothing on malaria drug, and in 2003, UNICEF only spent $ 1 million on the procurement of ACTs.[28] It is viewed that without the successful implementation of ACT in the next decade, significant progress in the control of malaria in Africa will be impossible.

Changing to the CST therapy, combined with rapid dipstick diagnosis to ensure treatment of only true malaria cases, for the estimated 168 million people currently treated with less effective drugs, would cost $ 6.5 billion and deliver benefits of $251 billion over the period 2001 – 2015. However, to meet the goal of halving the incidence of malaria, an additional 112 million cases need to be treated each year. The incremental cost for this is in the order of $8.2 billion, with additional benefits of $158 billion.[29]

4.3.2 Insecticide Treated Nets

The effectiveness of nets impregnated with synthetic pyrethroids (ITNs) is an effective tool in vector control. An increase in the use of ITNs from the current 2% to 70% in under-5's would provide a benefit of nearly $ 18 billion annually at a cost of $1.77 billion. An additional 60 million children would be protected in areas where malaria is endemic.[30]

The use of ITNs in preventing malaria varies with the level of malaria transmission. In areas of low or unstable transmission where biting takes place in early evening and morning, they do not work as well. Insecticide treated bed nets, promoted widely in Africa, have been shown to reduce bites from infected mosquitoes by up to 90%.[31] ITNs have furthermore been shown to reduce overall child mortality by

between 14 and 63% in various endemics settings.[32] ITNs however require high usage rates within a community to act as an effective public health tool.

The cost of an ITN is a major barrier to ownership. Usage for a large proportion of the affected population is low, with ITN coverage being generally higher in urban areas and in wealthier households. In most African countries, many more households have mosquito nets not treated with insecticides. Net and ITN possession and usage by children under the age of 5 is 2 – 3-fold lower in rural areas in comparison to urban areas. In Africa, the number of ITNs has increased dramatically due to the provision of free or subsidised ITNs for children under 5 and pregnant women.[33] Nevertheless, it has been found that even with the efforts of the RBM programme, only 1 in 7 children sleep under a net, and only 2% of all children use a net impregnated with insecticide.[34] The use of ITNs by pregnant women is also very low, with coverage in the region of 3%. Nets need to be retreated periodically to ensure that the insecticide remains effective. This adds a further cost. The scaling up of the re-treatment of ITNs with insecticide is hence also an important complement to the distribution and effectiveness of ITNs.

4.3.3 Intermittent Presumptive Therapy use for pregnant women

The integration of Intermittent Presumptive Therapy (IPT) into antenatal care services has become part of the national malaria control strategy in 21 countries. WHO recommends that IPT with an effective, preferably one-dose, antimalarial drug be made available to pregnant women as a routine part of their antenatal care in highly endemic areas. At present, SP given at therapeutic dose, is believed to have the best overall effectiveness in areas of high transmission, and low resistance to SP. Other antimalarials are being evaluated.

However, only 11 countries are in the actual process of implementing IPT for pregnant women. IPT coverage is fairly evenly distributed between urban and rural areas, and between less poor and poorer women. This is interpreted to mean that antenatal clinic services are widely used among all socio-economic levels in the African population. This hence provides a major opportunity for the delivery of IPT.

Providing antimalarial treatment to 90% of women in their 1st pregnancy is estimated to protect nearly 5 million mothers and their newborn infants annually. Over the period 2002 – 2015, this would costs less than $ 0.5 billion, and deliver benefits of $6.2 billion.[35]

4.3.4 Spraying with effective insecticides:

About half of the endemic countries, mainly in south and east Africa include targeted indoor residual spraying (IRS) in their malaria control strategy. An increasing number of countries are using IRS for mosquito control and the number of households sprayed has increased. Given the fact that many countries within the Southern African region fall in the unstable transmission category, vector control through residual house spraying is however a major strategy. Malaria control programmes are however constantly seeking alternative insecticide for use in IRS.

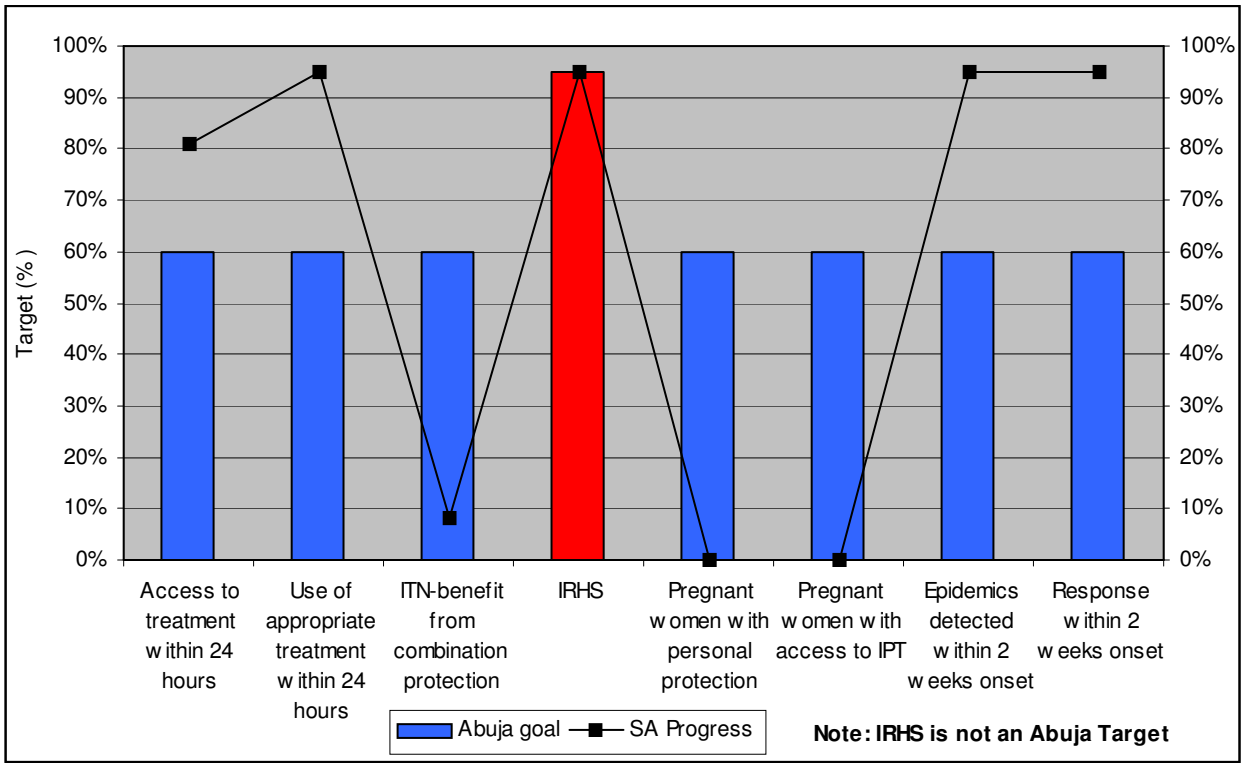
4.3.5 Intermittent Preventive Treatment in Infants

Research on intermittent preventive treatment in infants (IPTi) is still being carried out. This approach which has not yet been introduced into immunisation programmes, involves treating infants with an anti-malaria drug three times during the first year of life, at the time of routine immunisation. A study, supported by the Gates Foundation, completed in 2001 showed that the intervention reduced malaria incidence among infants by 59%, and halved the incidence of anemia.

4.4 SOUTH AFRICA

According to the most recent Health Systems Trust report, South Africa has surpassed the Abuja targets[36] for several indicators, including access to treatment.

Figure 4: South Africa's progress towards Abuja and National Goals, 2003



A RBM base line survey is yet to be conducted in South Africa, however data from a Heath Systems Trust desk review on provincial figures is available.[37] The treatment policies followed in South Africa are outlined below.

4.4.1 Access to prompt and effective treatment

The choice of first line antimalarial drug treatment has become controversial with many advocating early conversion to artemisinin-combination therapies. Others have suggested adding such products to drugs that retain some activity against the parasite. South Africa was the first African country to introduce the use of artemisinin based combination treatment (ACT) in 2001. In KZN during 2001, community based drug efficacy studies showed parasitological resistance levels to sulphadoxine-pyrimethamine (SP) greater than 62%. The drug policy was therefore changed to a fixed dose combination treatment Co-artem®, artemether plus lumefantrine.

In 2001, trials in the Limpopo province revealed a 5% resistance to SP, indicating an immediate change to the new drug policy. In Mpumalanga in 2002, 14% resistance to SP was revealed in drug tests; hence this province added a combination based (artesunate + SP) therapy to protect SP from further increases in resistance.

This change has contributed significantly to the decrease in malaria morbidity, mortality and transmission. The Department of Health treatment protocol for malaria in South Africa is hence through the use of combination based therapy, using the artemisinin based derivatives which conform with WHO drug policy.[38] The drug combination is effective against the asexual stage of *P. falciparum* and has a further effect blocking the transmission stage of the parasite.[39]

Healthcare facilities within the malarious regions are well stocked (95 – 100%) with antimalarial drugs. Hence access to treatment, subsequent to diagnosis, is not a concern. Provincial malaria programmes ensure that training and drug supplies are appropriate with the National Malaria Treatment policy. [40]

4.4.2 Insecticide Treated Nets

The use of ITNs is a strategy not widely used in South Africa. The coverage of ITNs is low, in the order of 3 – 5%. Indoor residual house spraying (IRHS) remains the major vector control thrust of the malaria control programme in South Africa.

Policy makers in South Africa have not adopted ITN as a main strategy for controlling malaria, although an ITN policy is being developed. Whilst studies have indicated that ITN interventions have a limited positive impact on malaria case reductions, the number of such studies in South Africa is limited.[41] The debate continues as to whether the implementation of ITNs should be as a complementary strategy or routine strategy, or in epidemic situations only.

4.4.3 Spraying with effective insecticides

Malaria vectors resistant to existing insecticides (*An. funestus* to synthetic pyrethroids) was discovered in KwaZulu Natal in 1999.[42] This necessitated a reversal to the use of DDT for house spraying. South Africa and 5 other African countries were given permission from the United Nations Environmental Programme (UNEP) to use DDT for public health use. This was after South Africa had signed the Stockholm convention on persistent organic pollutants in 2000. DDT is currently one of the insecticides used for IRS. Exceptions were given to developing countries on the condition that research for safe and alternative chemicals and non-chemicals would continue in order to find an equally efficient and affordable method for vector control. The use of DDT has resulted in the eradication of *An. funestus* (a potent transmitter of Malaria).

4.4.4 Intermittent Presumptive Therapy use for pregnant women

IPT for pregnant women in South Africa is not a priority as people living in malaria areas are rarely asymptomatic parasite carriers. It is viewed that in the South African context, this intervention may promote drug resistance and will not be cost-effective.

4.4.5 Lubombo Spatial Development Initiative - Collaboration with neighboring countries

South Africa is collaborating with neighbouring countries, Swaziland and Mozambique, within the framework of the Lubombo Spatial Development Initiative (LSDI), a Public Private Partnership (PPP), implemented in 2000. This project involves governments, business sector and communities. Funding for the first 2 years of this project was *via* The South Africa Business Trust (R4.6 million), Mozal, The Department of Health in South Africa, and the Ministry of Health in Mozambique. The 5-year programme was estimated to cost R 40 million.[43] The programme has recently been awarded a grant of US$22 million over the next 5 years by the Global Fund to fight AIDS, TB and Malaria.

The geographic region targeted by this initiative is defined as eastern Swaziland, southern Mozambique and North Eastern KwaZulu Natal. These regions are linked by the Lubombo Mountains. The programme is run by the Regional Malaria Control Commission (RMCC) comprising the malaria control programme managers from the three countries, public health specialists and scientists. The RMCC is chaired by the South African Medical Research Council Malaria Research Programme.

Baseline surveys conducted by the RMCC in 1999 revealed that there was a marked difference in prevalence rates between the three countries. The lowest infection rates were in Swaziland ranging between 1% to 5%. In the KwaZulu Natal region, the prevalence range was 9 – 42%, and in Mozambique between 22% and 90%. Annual surveys of *P. falciparum* infection prevalence are conducted as part of the programme. The objective over 5 years is to reduce the prevalence of P*. falciparum* in Maputo province, believed to be the most affected region in the initiative, from 600 – 1,000 to less than 200 per 1,000. In South African and Swaziland it aims to reduce the incidence from 250 per 1,000 to 1 per 1,000. This will have a positive impact on socio-economic development in the region.

Malaria control in Swaziland is carried out by the Swaziland malaria control programme and in KZN by the KZN malaria control programme. Both use insecticide residual house spraying as control methods. IRS methods were introduced by the LSDI programme in the southern Mozambique in late 2000 where spraying had previously been confined to Maputo city. The LSDI has achieved malaria incident reductions of 96% in KZN, 91% in Swaziland, and 86% in participating areas of Mozambique.[44] This is attributed to the change of first-line treatment to co-artemether, the re-introduction of DDT spraying, as well as the regional approach to malaria control in the LSDI. The LSDI now protects approximately 4.7 million people in 1.8 million houses over an area of 100,000 km^2. Parasite prevalence in children between the ages of 2 and 15 was between 60 – 70% when the programme started, it is now less than 5%.[45]

4.4.6 Conclusion[46]

The South African Malaria Control Programme has clearly managed through the various intervention programmes to decrease the incidence of malaria annually. Malaria has been restricted to the areas bordering neighbouring countries. Malaria transmission in Limpopo is largely limited to the border with Zimbabwe and Mozambique. Strategies to address cross border malaria control between the Limpopo area and Mozambique are expected to have a similar impact on malaria reduction in South Africa as the achievements of the LSDI malaria initiative. The Department of Health is in the initial stages of setting up a cross border malaria initiative with Zimbabwe.

The resultant control has been followed by significant economic development, in some cases opening up previously uninhabitable areas for agriculture, mining and industry. The challenge in the long-term is to maintain this trend. Factors that will continue to influence the transmission of malaria are: climate variation, social change, cross-country collaboration and other factors such as drug and insecticide resistance.

The South African Health Systems Trust review states some of the challenges facing the malaria programmes in South Africa are as follows:

- Population movement across borders is likely to increase as South Africa's economy grows. Parasite and vector transmission is therefore viewed as highly likely.
- The monitoring of vector resistance to insecticides is critical to prevent future epidemics.

- The monitoring of drug resistance is also vital in light of the rapid development of parasite drug resistance recently experienced in South Africa.
- As the type of housing structures in rural areas changes from mud huts to western style, coupled with increasing insecticide resistance levels in malarious regions, alternative insecticides and/or alternative vector interventions will be required.

With these new challenges, the Health Systems Trust concludes that the malaria programmes will need to strengthen the range of interventions available at district level. Alternative vector control methods may be necessary, based on sound, scientific evidence.

5 SOCIOECONOMIC IMPACT

Within Sub-Saharan Africa, malaria is a major impediment to socio-economic development and is a major contributor to poverty. It has been well documented that malaria and poverty are inter-linked, it is understood to be both a disease of poverty and a cause of poverty. There is also evidence that effective malaria control is a positive precursor to development.

The burden of malaria is highest amongst the poor, as they generally have the least resources for control efforts and often cannot afford to seek treatment. They generally have little access to health and other social services, and have low levels of literacy. Malaria epidemics are therefore most likely to be most severe in the poorest communities. Furthermore, in many of these countries, exposure to malaria of the most vulnerable population groups is increased by migrations caused by poverty and/or conflict. A survey in the rural areas of Tanzania showed that the under-5 mortality following acute fever was 39% higher in the poorest socio-economic group than in the richest.[47] Another survey in Zambia showed that there was a substantially higher prevalence of malaria infection among the poorer population groups.[48]

Malaria affects the health and wealth of nations and individuals as it has an impact on many levels of the economy from the household, to the government and the macro economy. [49]

- Within **households and communities**, prevention and treatment costs are direct economic costs. Poor families in endemic areas such as northern Ghana have been estimated to spend up to 34% of their annual income on malaria prevention and treatment, in comparison to only 1% in rich households.[50] In another sample of households with a mean annual income of $ 115, the cost of malaria treatment added to the lost income of adult morbidity and caretaking for children with the disease represented about 20% of annual income.[51] Indirect economic costs include reduced income due to inability to work, and in the extreme case loss of income due to death. Social costs include sickness and death. Malaria will also affect the level of education as it causes absenteeism from school and scholastic performance

- The socio-economic impact on the **government** is related to the use of resources. Departments of Health must cover the costs of prevention and control, hence the direct costs of malaria include the money spent on health facilities, mosquito control and malaria-related education and research. Malaria can account for up to 40% of total government spending on public health.[52] In addition, the burden in this sector stretches to the use of medical staff to treat patients, thus potentially reducing the standard of care received by other patients.

- In the **private** sector, businesses likely to be affected include tourism, agriculture, mining and construction. Productivity declines and the costs of sick pay increase, in the long-term leading to declining profits and reduction in company performance. In addition, the threat of malaria can negatively affect visitors to the country.

Ultimately, malaria has a burden on Sub-Saharan Africa's economic performance. The combined impact of the above factors, will negatively affect the gross domestic product and socio-economic development is delayed. It has been estimated that malaria can account for an average annual reduction of 1.3% in economic growth for countries with a high disease burden.[53] UNICEF states that malaria costs Africa between US$ 10 – 12 billion annually in lost gross domestic product.[54]

A study in 2000[55] indicated that most economic estimates however neglect the impact of other short-term costs and long-term consequence such as:

- The economic cost of pain and suffering associated with malaria

- Increased treatment costs associated with spread of drug resistance
- Retarded physical and cognitive development in children and diminished attendance at school
- Malaria is also a major cause of anaemia in children and pregnant women, low birth weight, premature birth and infant mortality. Malaria also potentially increases vulnerability to other diseases

The short-term costs are therefore likely to result in economic losses of several percent of GDP per annum. Malaria hence hinders long-term economic growth, and hence the burden of disease will increase over time as countries do not experience the increase in living standard they would if malaria were not present.

5.1 MALARIA and the BURDEN on the HEALTH SYSTEM:

In sub-Saharan African countries, actual reported case rates represent only a fraction of the actual burden of malaria. Access to clinical care is poor, particularly in the most rural areas where malaria transmission is most intense. Malaria tends to be diagnosed clinically, with laboratory confirmation rarely available. Demographic and health surveys and other sources have indicated that less than 40% of malaria morbidity and mortality is seen in health facilities.[56]

In endemic African countries,[57] in children under 5 years of age as well as all age groups, 25 – 35% of all outpatient visits are for clinically diagnosed malaria. The Integrated Management of Childhood Diseases and the RBM recommend that in areas of high malaria endemicity, all acute fevers in children under 5 be treated presumptively with an antimalarial. Throughout the central, east and western African regions, about 30 – 35% of children under 5 report a fever in the 2 weeks preceding the survey. Hence, although many childhood fevers are not malaria related, they do determine the demand for antimalarial drugs. Malaria accounts for 20 – 45% of hospital admissions, and 15 – 35% of hospital deaths amongst inpatients due to late presentation, inadequate management and unavailability or stock-outs of effective drugs. Malaria is thus an important contributor to the demand for health care in children under the age of 5.

The high burden of malaria may to some degree be as a result of misdiagnosis, due to the reliance on clinical diagnosis the disease is often difficult to distinguish from other infectious diseases. Clearly however, malaria is responsible for a high percentage of public health expenditure on curative treatment. Malaria hence imposes an enormous burden on an already widely stretched healthcare system. Malaria thus continues to be a major impediment to health in Africa south of the Sahara.

5.2 MALARIA and INDUSTRY:

The costs involved in the control of malaria also have an effect on discouraging foreign trade and investment. International corporations seeking to extract natural resources may be willing to invest in intensive malaria control measures as the value from the natural resources outweighs the cost. In Zambia for example, such investments in malaria control greatly increased the output from the copper mines.[58] The Konkola Copper Mine in the Konkola highveld belt in northern Zambia financed and run an effective campaign to protect its workers and the community against infection. The programme halved the number of malaria cases among the 350,000 people living in a 2,700 km^2 zone. Similarly, commercial operations including BHP Billiton operating an aluminium smelter in Mozambique became involved in the LSDI programme to control malaria in the Lubombo region with success as has already been outlined.

Investors may well however choose to invest in malaria-free areas. To encourage investments in the kinds of manufacturing industries that have formed the basis of growth in many developing countries, it is thus necessary to provide an environment that can compete with other such opportunities. Hence, in a developing nation, malaria can prove economically costly in the long-run.[59]

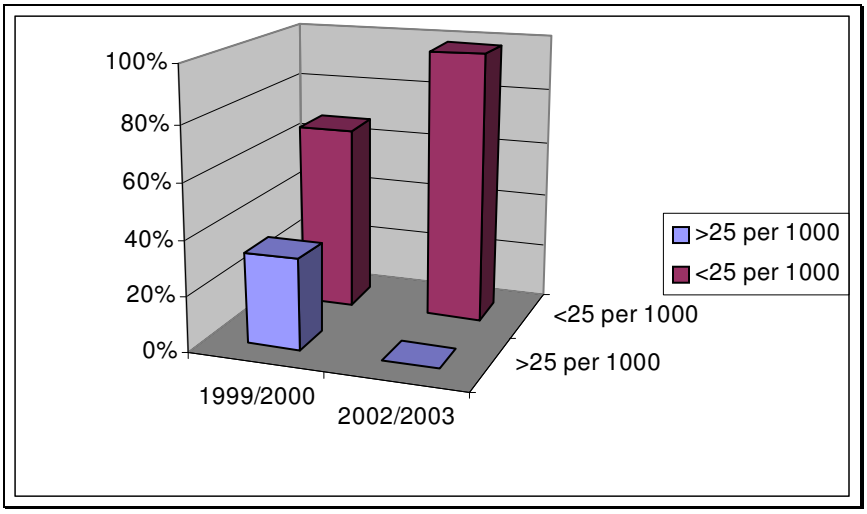
Malaria also has an impact on trade within a country as visitors to malarious areas have no acquired immunity. This may therefore inhibit the development of industries which often form the building block of economic growth. Within the South African context for example, the travel and tourism industry is the fourth largest contributor to foreign exchange, with a huge potential. Its total contribution to South Africa's GDP in 2002 was 7.1%, with a contribution of approximately R 110 billion. It is the fastest growing economic sector in South Africa, and is very labour-intensive hence stimulating a broad range of other industries. For many years however, malaria has been a hindrance to development. Tourists require virtually complete protection against contracting malaria. The mere perception of a risk of malaria, severely impacts on the potential for tourism growth.

Research has shown that the high rates of malaria in the Lubombo area, is one of the major causes of ongoing underdevelopment and poverty.[60] In 1999, the incidence of malaria in KZN was in excess of 27,000 cases. In that year the Lubombo Spatial Development Initiative (LSDI) was signed. It was stated at the time, that the promotion of agriculture and tourism in the region would only be effective provided that the risk of being infected with malaria had declined substantially, and that there was an ongoing malaria control programme in place.

A study by the LSDI Malaria Control programme was thus initiated to determine the influence of malaria on tourism and the effects of malaria control on development in the area. Tourist facility owners and managers were the focus of this study, which was carried out by the Medical Research Council.[61] The survey of 86 tourist facilities in the area during 2000/2001 confirmed that malaria was perceived as the principle negative factor determining occupancy. Cancellations were on average 44% during the 2000 malaria season, due to the floods experienced leading to a concern about potential epidemics.

The graph below shows the effects of malaria control on the LSDI area as it pertained to tourist facilities.

Figure 5: Location of Tourist facilities in the LSDI area



This graph clearly indicates that in the 1999/2000 season, 67% of tourist establishments were located in an area of less than 25 per 1,000 infections, 33% were in areas of more than 25 per 1,000. In 2002/03, 98% of the tourist venues were in areas with infection rates of less than 25 per 1,000. The possibility of becoming infected with malaria has thus decreased significantly, which is anticipated to have a positive effect on tourism in the Lubombo corridor. In an indication of its confidence in the area, in 2003 the government announced 8 new tourism projects worth R 430 million in the Lake St Lucia area.

6 CONCLUSION

Malaria has a massive impact on human health; with around 40 % of the world's population at risk. Around 300 - 500 million clinical cases occur each year resulting in between 1 – 2 million deaths, the majority in sub-Saharan Africa. The societies and economic development of some of the world's poorest nations are severely affected by malaria. The most deadly of the four *Plasmodium* species that cause human malaria is the protozoan parasite *P. falciparum,* the species most common in Africa. Malaria is Africa's second biggest killer after HIV/AIDS.

The focus of malaria control programmes internationally is on the provision of effective and affordable interventions and the management of infected children through early treatment with effective antimalarial drugs. The need for new and improved tools is nevertheless an ongoing concern as is a better understanding of the disease and its processes, and the effective application of existing technologies. Within the context of the Initiative's proposed activities, the need for better tools is in three areas.

New drugs with high effectiveness, simple regimes and low toxicity to counter the spread of drug-resistant strains of malaria

Combination artemisinin therapies are the most effective antimalarial treatment available at present. They are however obtained from processed plants, *Artemesia annua*, and their production is lengthy and relatively costly. The cost of the most effective ACT is $2.40 per treatment. Although it is sold to the public sector at cost, the treatment is still significantly more expensive than the traditional first-line drugs. The quality and stability can also be an issue. Scale-up requires more farmland, dedicated extraction facilities and is relative cost effective. The development of cheaper ACTs with more complete safety data is therefore a priority.[62] Furthermore, control strategies based on early treatment require a continual search for new drugs before the malaria parasites develop resistance. The long-term strategy should therefore be to interrupt the transmission of the parasite.[63]

Efficacious environmental control mechanisms aimed at the mosquito vector

Insecticide resistance is a major problem facing control programmes in most countries and residual house spraying is however compromised by the fact that choice of alternative insecticides to DDT is limited. Furthermore, in many areas where the use of ITNs is deployed and the benefits are considerable, community take-up is disappointing. The use of insecticide treated bed nets has therefore been implemented with variable rates of success. There is therefore potential for research into improving the effectiveness of control methods. Work therefore remains to be done on various insecticide-fabric combinations, as well as on technology to permanently impregnate the nets.[64]

Rapid and reliable diagnostic tests that can be used among populations with limited access to health facilities:

In most areas of the developing world, malaria is not confirmed by laboratory diagnosis, potentially contributing to the growth in resistance. The inability to diagnose malaria quickly contributes to increased mortality, prolonged morbidity and delayed response to emerging epidemics. Dipstick tests and other rapid, user-friendly diagnostic tests that are sensitive and specific for those areas that do not have access to laboratory apparatus are essential for meeting these challenges.

The completed genomes of *P. falciparum* and its vector *An. gambiae* therefore open up new approaches to the development of drugs, vaccines, insecticides and insect repellents, as well as intervention into malaria transmission. Genetic tools will also allow the sampling of parasite, mosquito, and human genomes in malaria affected areas to support the malaria control activities. The combination of these tools is therefore essential in the battle to halt transmission of malaria in Africa and other endemic areas of the world.

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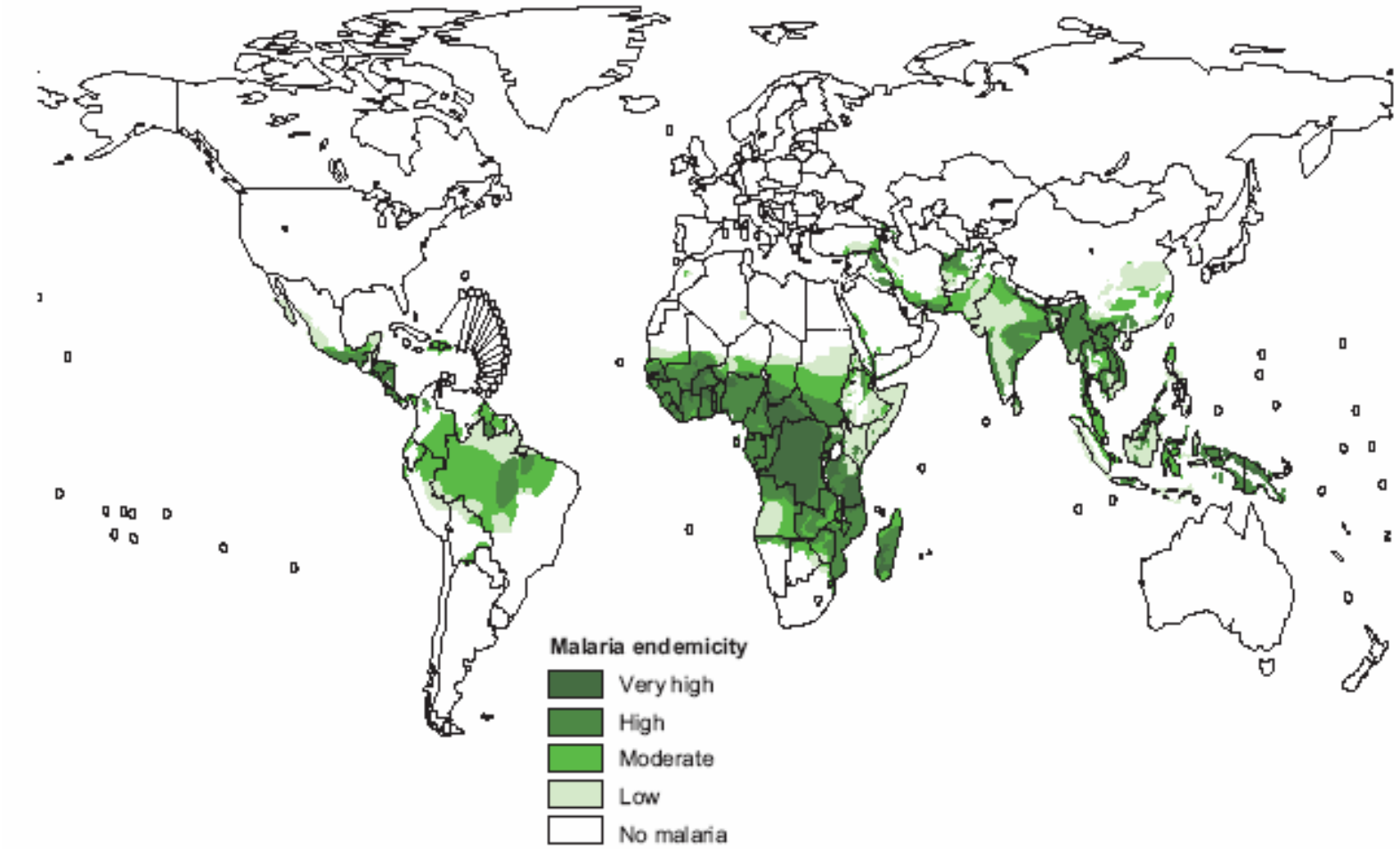
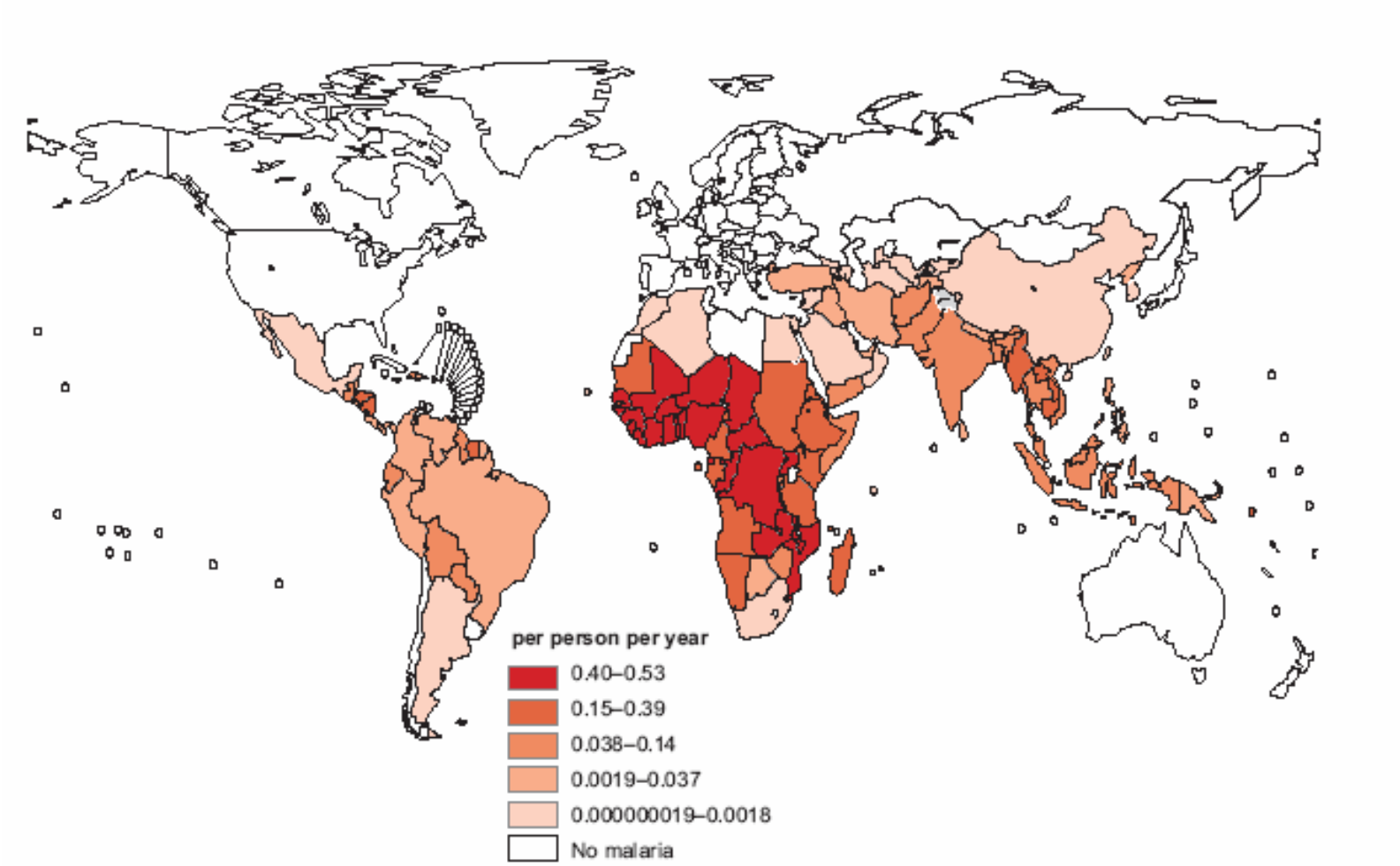
APPENDIX 1
Global distribution of malaria transmission risk, 2003



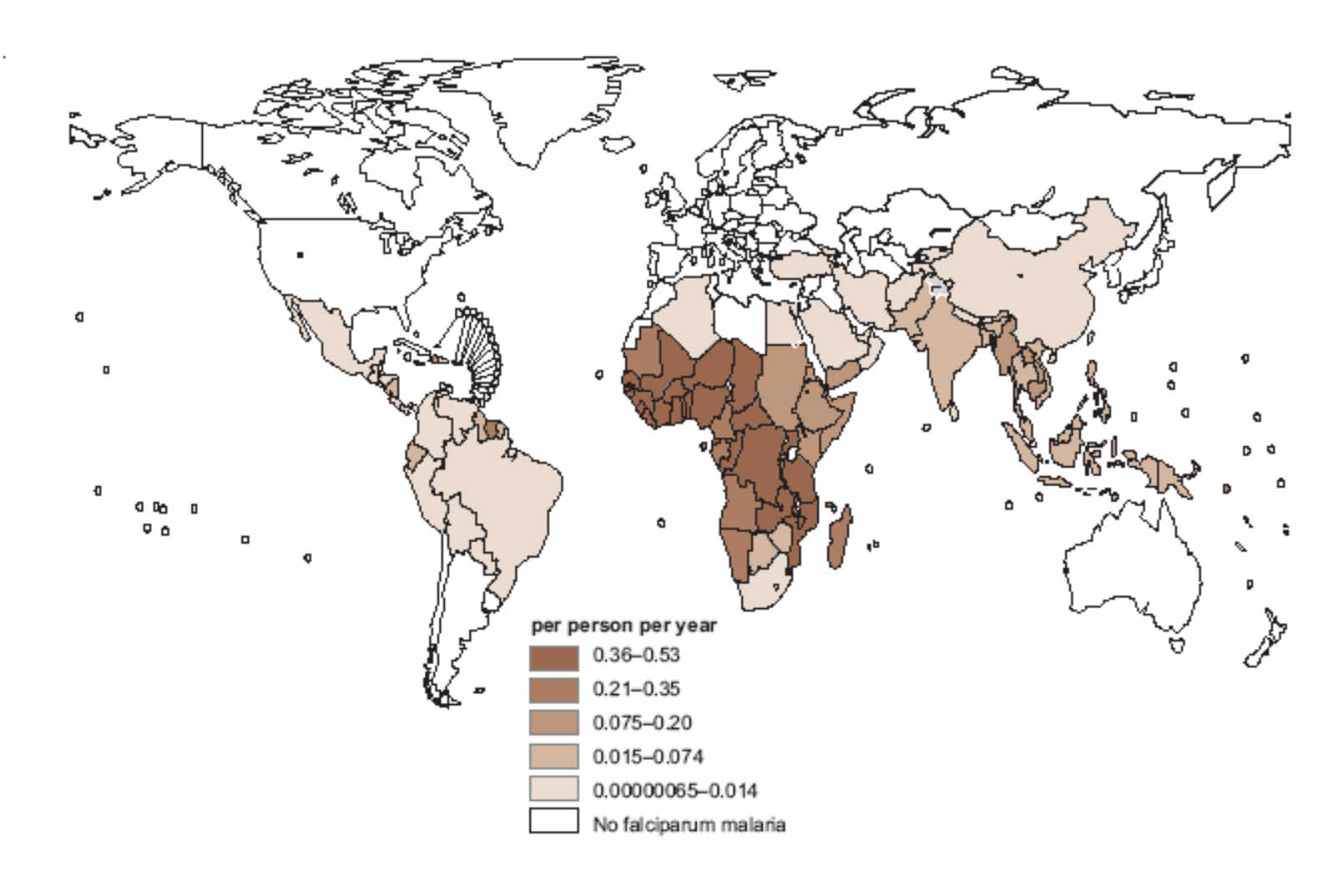
Reference: World Malaria Report 2005

APPENDIX 2
Estimated incidence of clinical malaria episodes (all species) 2004



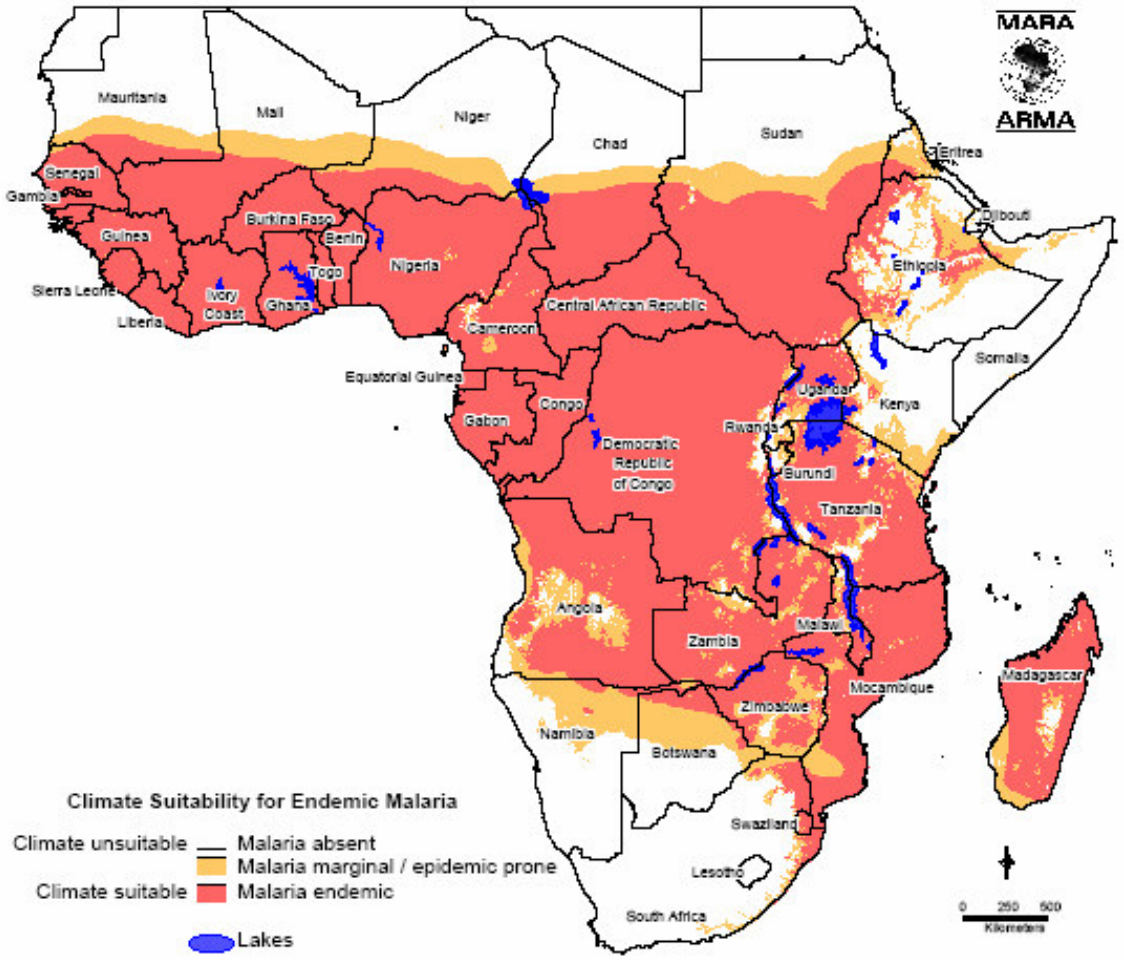
Reference: World Malaria Report 2005

APPENDIX 3
Estimated incidence of clinical *P. falciparum* episodes 2004



Reference: World Malaria Report 2005

APPENDIX 4
Distribution of Endemic Malaria in Africa



This map is a product of the MARA/ARMA collaboration (http://www.mara.org.za). July 2001, Medical Research Council, PO Box 17120, Congella, 4013, Durban, South Africa
CORE FUNDERS of MARA/ARMA: International Development Research Centre, Canada (IDRC); The Wellcome Trust UK; South African Medical Research Council (MRC); Swiss Tropical Institute, Multilateral Initiative on Malaria (MIM) / Special Programme for Research & Training in Tropical Diseases (TDR), Roll Back Malaria (RBM).
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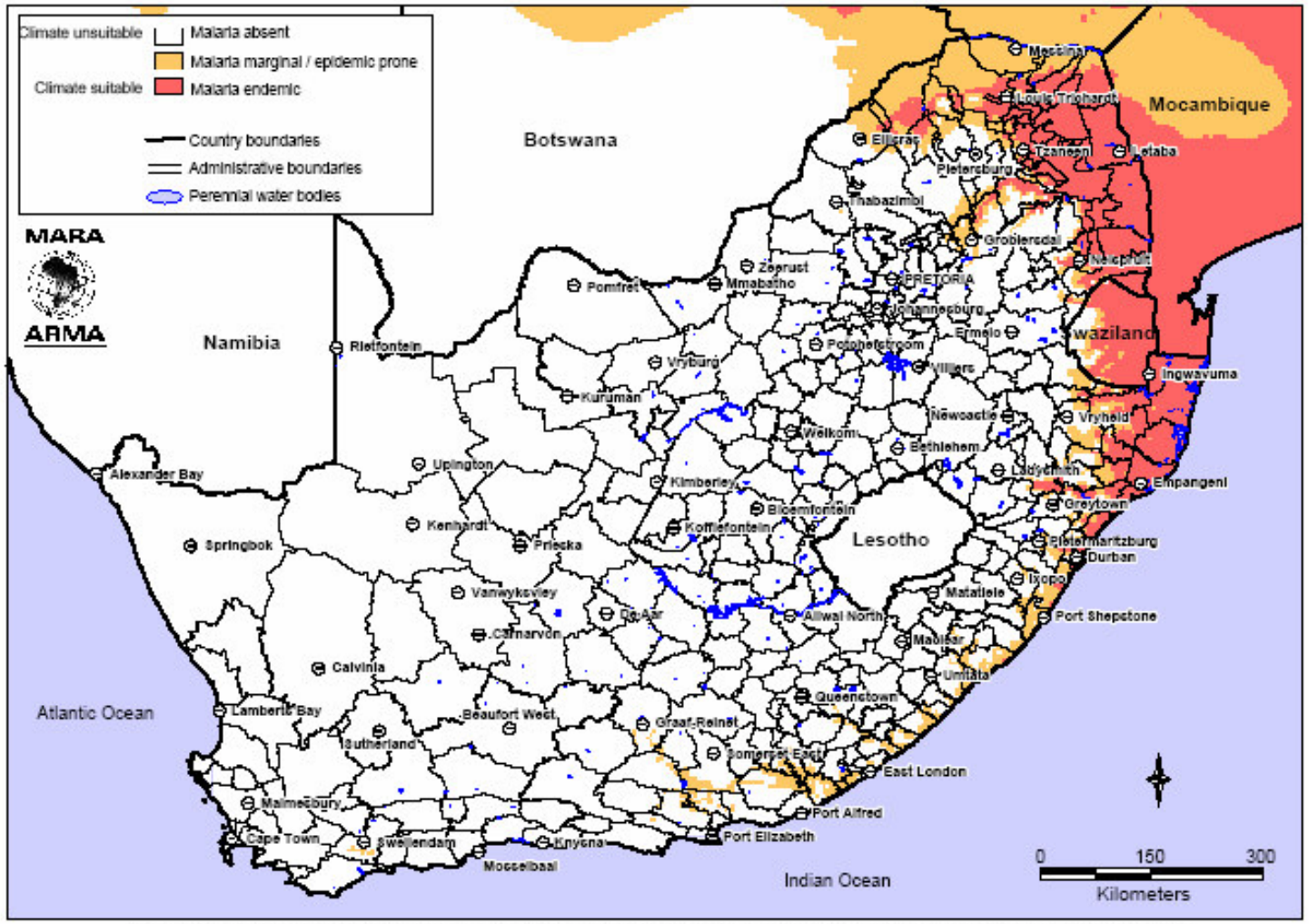
APPENDIX 5
South Africa: Distribution of Malaria



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