# Malaria control in South Africa – challenges and successes

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Control measures have substantially reduced the historical distribution of malaria in South Africa; the country's population currently at risk for contracting malaria is approximately 4.3 million, predominantly in the northern and eastern border areas. The major strategies for malaria control are vector control through indoor residual spraying, case management, disease surveillance, epidemic preparedness and response, and public awareness. There has been a significant and sustained decrease in malaria case notifications since 2000, as a result of intensive indoor residual spraying including the use of DDT to combat insecticide-resistant *Anopheles funestus*; the introduction of artemisinin combination therapy; and the Lebombo Spatial Initiative, a cross-border collaboration targeting malaria in eastern Swaziland, southern Mozambique and northern KwaZulu-Natal (KZN). Rapid malaria antigen detection tests are widely used for diagnosis at primary health care level. HIV-malaria co-infected patients who are malaria non-immune are at risk for severe malaria. Renal failure has been identified as a particular complication in this group of patients. Despite successes in malaria control in South Africa, many challenges remain.

## Background

Africa presents with the world's highest malaria incidence: 85% of cases and 90% of malaria-related deaths.[1] The continent is home to the most efficient vector mosquitoes in the world, the climate of much of sub-Saharan Africa is suitable for transmission, socio-economic factors constrain spending on national treatment and control measures, much of the population is poor and rural with little access to curative or public health measures, and resistance to antimalarial drugs and insecticides is rife.[2] In many African countries, the ready availability of antimalarials without prescription, and incompleted treatment courses, contribute to drug pressure, and the range of antimalarial drug options is limited. HIV has worsened the effects of malaria in many respects, depending on the degree of acquired immunity.

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## Malaria in South Africa

Africa has a spectrum of malaria epidemiology ranging from intense year-round transmission to unstable, epidemic-prone areas. South Africa is fortunate in several ways regarding malaria: it is at the southern extreme of malaria distribution in Africa; relatively small areas experience seasonal transmission (hence malaria is unstable and epidemic-prone);[3] a well-organised national malaria control programme exists; and the country has a relatively well-developed scientific, economic and health infrastructure.

### History of malaria control in South Africa

Malaria was recognised as a major cause of illness and death by early settlers and travellers in southern Africa. In the mid-19th century, the early pioneers leaving the non-malarious Cape Province soon experienced the menace of malaria in the northern Transvaal. Gear[4] wrote:

'In South Africa, prior to the implementation of malaria control, transmission extended as far south as Durban and even Port St Johns, and inland as far as Pretoria during favourable years, causing large epidemics with up to 20 000 deaths. During the 1930s the indoor feeding habits of malaria vectors were recognized and indoor space spraying with pyrethrum on a weekly basis was introduced. Together with oiling of suitable larval habitats a considerable degree of control was achieved. The breakthrough came with the availability and use of DDT and other long-lasting insecticides from 1945 which replaced the pyrethrum spraying and resulted in a dramatic interruption of malaria transmission in virtually all areas, with the disease becoming restricted to parts of the north-eastern low-lying areas, and the vector *Anopheles funestus* being eradicated. Active surveillance of malaria infections and treatment was intensified in the 1960s, further decreasing malaria transmission. Drs Annecke, Park-Ross and Botha de Meillon were among those responsible for these achievements.'

### Epidemiology of malaria in South Africa

Malaria is endemic in the low-altitude areas of the northern and eastern parts of South Africa along the border with Mozambique and Zimbabwe, with transmission taking place mainly in Limpopo, Mpumalanga and KwaZulu-Natal provinces, and occasionally in North West province. The population at risk for contracting malaria in South Africa is approximately 4.3 million. The major strategies for the Malaria Control Programme in South Africa are vector control through indoor residual spraying, case management, disease

surveillance, epidemic preparedness and response, malaria advocacy, and information, education and communication.[5]

There has been a significant and sustained decrease in malaria case notifications, from 64 622 cases in 2000 to around 8 000 in 2006, as a result of a number of initiatives, among which are intensive indoor residual spraying including the use of DDT to combat insecticide-resistant *A. funestus*, the introduction of artemisinin combination therapy (ACT) for treatment of uncomplicated malaria,[6] and the Lebombo Spatial Initiative, a cross-border collaboration targeting malaria in eastern Swaziland, southern Mozambique and northern KZN.[7,8]

### Vector control in South Africa

Historically, malaria control in Africa has relied mainly on residual insecticide spraying of houses, capitalising on the feeding and resting behaviour of vectors. Its success depends on the assumption that the vectors bite humans indoors then rest on the walls. This is true of the two major vectors *A. gambiae* and *A. funestus* (and resulted in the elimination of the latter from its former range in South Africa). *A. arabiensis*, with its wider range of behaviours, can be controlled but not eliminated with residual spraying of houses. Residual spraying is labour-intensive and expensive, and requires a strong vertical programme to maintain efficiency. It has been highly successful in South Africa but has not been sustainable on a wide scale elsewhere in Africa. *A. arabiensis* breeds in small, sunlit temporary pools such as cattle hoofprints, and is not amenable to larval control, unlike *A. funestus*, which prefers more permanent water. The latter vector species, highly susceptible to residual house spraying for the above reasons, had been eliminated from the malaria transmission area in KZN many years previously. In 1996, bowing to international environmental pressure, the South African malaria control programme replaced DDT with synthetic pyrethroid insecticides. The incidence of malaria in the area rapidly increased five-fold to around 60 000 cases per year; a confounding factor was widespread resistance to sulphadoxine-pyrimethamine (SP – Fansidar), which had been used as first-line treatment for the previous decade. In 1999, pyrethroid-resistant *A. funestus* was found resting indoors in sprayed houses – an invasion from neighbouring Mozambique.[9,10] A change in first-line treatment from SP to artemether-lumefantrine (Coartem) and reversion to DDT house-spraying has brought the malaria incidence to normal levels.[7,8] This illustrates the importance of clinical and laboratory monitoring of antimalarial drug resistance in the parasite, and the entomological monitoring of vectors and insecticide resistance. More recently, in 2006, the World Health Organization (WHO) gave its full support and advised the use of DDT for indoor residual spraying.

## Malaria management

There are four species of plasmodia that infect humans. *Plasmodium falciparum* accounts for the majority of malaria cases in southern Africa and is the predominant species associated with severe and fatal disease. Almost all South Africans are non-immune, including residents of seasonal malaria transmission areas, and are therefore at risk for developing severe malaria. Early, effective case management is one of the cornerstones of malaria control. The sustainable supply and rational use of effective antimalarials is required both for clinical cure and for reduction in malaria transmission. The choice of chemotherapy for malaria is dependent on the severity of disease, the known or suspected resistance pattern of the parasite in the area where the malaria infection was acquired, the species of parasite, patient characteristics (age, pregnancy, co-morbidity, allergies, other medications) and the presence or absence of vomiting. It is recommended that patients receive prompt treatment with the most effective treatment regimen available. Drug choices may change over time depending on development of parasite resistance and availability of other anti-malarial treatment.[6] Chloroquine (CQ) was the mainstay of antimalarial treatment and prevention for many decades after its widespread use began in the 1940s. Starting in 1959 in two foci – South America and Southeast Asia – chloroquine resistance (CQR) has gradually spread to most of the tropical world, sparing only parts of Central America, North Africa, the Middle East and East Asia. The most significant area affected by CQR is sub-Saharan Africa, which represents 90% of the world's malaria mortality.

Parasites with low-level CQR may still show partial responses to CQ treatment, especially in those patients who are semi-immune. Chloroquine is therefore still used as it is cheap, but it is not reliable for treating severe malaria or malaria in non-immunes. By 1988, CQR was a significant problem in KZN, leading to treatment failures and necessitating a change to SP as first-line treatment for uncomplicated malaria. The provinces of Mpumalanga and Limpopo followed suit in 1997 because of rising CQR.[11] By 2001, SP resistance in KZN necessitated a further change and was replaced by artemisinin combination therapy (ACT) in the form of artemether-lumefantrine. Together with the re-introduction of DDT for indoor residual spraying, this led to a profound reduction in malaria incidence, hospital admissions for malaria-related illness, and mortality.[7] Although resistance to SP remained low, Mpumalanga and Limpopo provinces changed to ACT in 2003 and 2004 respectively, in accordance with the WHO recommendations for the use of combination therapy.

The use of monotherapy for malaria throughout the world has resulted in the development of parasite resistance to sequential single-drug regimens. The concept of combination

therapy for malaria is based on the potential of two or more simultaneously administered schizontocidal drugs with independent modes of action to improve therapeutic efficacy and also to delay the development of resistance to the individual components of the combination. A strategy is to design the combination so that one drug (typically an artemisinin derivative such as artemether) acts extremely rapidly to dramatically reduce the parasite load, and the other is longer-acting (e.g. lumefantrine, SP) to mop up any surviving parasites. In such small surviving numbers of parasites, the probability of resistant mutants occurring is much lower than at the start of combination therapy.[12,13] Artemisinin-based combination therapy (ACT) is now generally considered as the best current treatment for falciparum malaria. ACTs have the advantages of rapid clinical and parasitological response, improved cure rates, decreased malaria transmission and the potential to delay antimalarial resistance.[13] Artemether-lumefantrine is the only ACT currently registered in South Africa.

The artemisinins are derived from the wormwood plant, *Artemesia annua*, which has been used in China to treat fever for 3 000 years. The active ingredients were identified in 1970, and a number of derivatives of this compound have been used successfully in the treatment of drug-resistant *P. falciparum* malaria. These include artemether, artesunate and dihydroartemisinin. They differ in their efficacy, absorption, bioavailability and toxicity. The artemisinins are the most rapidly acting antimalarial drugs, and clear parasites rapidly from the peripheral blood and have a broad stage of action. They are well tolerated, have a favourable safety profile, and are highly effective against both uncomplicated and severe *P. falciparum* infections as well as the blood stages of *P. vivax* infections. Limited safety data preclude routine use in pregnancy. Artemisinins may reduce malaria transmission in medium-risk areas by decreasing gametocyte development, but this advantage has yet to be demonstrated in high transmission areas. When used as single-drug therapy for short periods, recrudescence is common, and therefore these drugs should always be used in combination with a longer-acting antimalarial.[13,14] Quinine remains an alternative to ACT for treatment in South Africa. Resistance has been slow to develop in South America and Southeast Asia, and high-grade resistance has never been well documented. Cure rates in SE Asia are declining, and it is now usually given in combination with the antibiotics doxycycline or clindamycin, which also have antimalarial activity.

## Diagnosis of malaria

The prompt and accurate diagnosis of malaria is important because of its potential for rapid and serious clinical deterioration to complicated and possibly fatal disease states. Three components contribute to an optimum diagnostic outcome: awareness, which includes taking an adequate travel history and also remembering that malaria transmission occasionally occurs outside endemic areas (Odyssean or airport malaria, and needle and transfusion malaria); clinical astuteness and experience; and laboratory tests. Microscopy of blood smears stained with Romanowski stains (Giemsa or similar) is the traditional laboratory method and is still the mainstay of diagnosis. It requires skill and experience that is not always available, and modern technology has provided rapid tests, based on lateral-flow immunochromatographic ('dipstick') detection of malaria antigens, that are suitable for use by persons without specific laboratory training. Most commercially available tests detect the *P. falciparum* histidine-rich protein 2 (PfHRP-2) antigen; pan-specific antigens such as lactate dehydrogenase or aldolase will detect other species as well, with variable sensitivity.[12,15,18] Limited accessibility to laboratories for the rapid diagnosis of malaria in the rural areas of South Africa, particularly with a need for a definitive malaria diagnosis with the use of more expensive treatment options, led to the introduction of rapid malaria tests in rural clinics and health centres.[16] These tests are highly sensitive and specific for *P. falciparum*, but results are highly dependent on the quality of the rapid test, and appropriate storage, use and interpretation in the field.[16] The WHO is working on systems to improve rapid test kit pre-accreditation evaluation and post-production quality testing. Molecular techniques such as the polymerase chain reaction (PCR) are normally not suitable for routine diagnosis of malaria, but are important tools for epidemiological and parasitological research. The advent of automated DNA extraction and real-time PCR may change this situation soon, but expense is likely to remain a constraint for widespread use of PCR.

### Severe malaria

*P. falciparum* infections may progress rapidly to a fatal multi-system disease. The key factors in preventing severe malaria are early and accurate diagnosis and urgent treatment with effective drugs. In areas of high transmission in Africa, the highest mortality is in infants, while adults are largely semi-immune. In South Africa, because of much lower transmission intensity, all age groups are vulnerable to severe disease. Complications can develop rapidly within 48 hours of the onset of malaria disease in any non-immune person, but especially in young children and pregnant women. Immunocompromised patients and those without a functioning spleen are also at risk for severe malaria. The clinical manifestations of severe malaria depend on the age of the patient. In children, hypoglycaemia, convulsions, and severe anaemia are relatively common, while acute renal failure, jaundice, and ARDS are more common in adults. Cerebral malaria, shock and acidosis may occur at any age. Pregnant woman are particularly at risk for hypoglycaemia, anaemia, and ARDS, as well as fetal loss.[6,17]

Currently, intravenous quinine is the only treatment available in South Africa for patients with severe malaria. However, intravenous artesunate has been shown to reduce mortality from severe malaria by 34.7% (15% mortality with IV artesunate v. 22% with IV quinine) in a large ($N$=1 461, including 202 children) randomised controlled trial, in addition to its other advantages of rapid action in terms of parasite clearance, safety and ease of administration. Thus, for every 11 to 20 patients with severe malaria treated with IV artesunate instead of IV quinine, an additional life is saved.[18] The WHO now recommends this as the treatment of choice for severe malaria in adults. Multi-centre randomised controlled trials are currently being conducted to compare intravenous quinine and artesunate in African children with severe malaria.

Mortality and morbidity studies in South Africa have identified the following as the main causes of unfavourable outcome: late presentation to health facilities, particularly in patients in low-risk areas; those with co-morbid disease, especially HIV co-infection; failure to consider malaria as a cause of fever; and poor management of malaria-related complications.[19,20]

Resistance builds up rapidly in malaria parasite populations when they are exposed to long periods of sub-therapeutic levels of antimalarials. Monitoring for drug resistance and safety is an essential component of any national drug policy when new drug regimens are introduced. In South Africa, the South East African Combination Anti-malarial Therapy (SEACAT) initiative was established at sentinel sites and aims to monitor resistance. Clinical and parasitological response to treatment is monitored in a cohort of patients. With the major decrease in malaria cases, measuring molecular surrogates of resistance may act as a guide to the development of resistance. The major effects of antimalarial drug resistance are progressively increasing morbidity, mortality and transmission, as well as increased costs, potential toxicity and side-effects, and concerns about efficacy of the alternative drugs. There is a very limited range of available alternative agents, hence the growing recognition of the importance of careful selection of combinations of drugs that will delay the emergence of resistance.[21]

### HIV and malaria

Large numbers of HIV patients live in areas where malaria is endemic or where there is risk of unstable malaria. The interaction between the two diseases is unclear. HIV-infected patients who develop malaria may present late to health centres, and the diagnosis may be missed because of symptoms common to the two diseases. HIV-infected individuals who live in malaria endemic areas and who may be malaria semi-immune, are at increased risk of symptomatic parasitaemia and/or may exhibit higher levels of peripheral parasitaemia than semi-immune adults who are HIV-negative. HIV-malaria co-infected patients who are malaria non-immune are at risk for severe malaria. As HIV progresses and immunosuppression worsens, the risks of severe malaria increase. Renal failure has been identified as a particular complication in this group of patients. It is unclear how HIV infection modifies the therapeutic response to antimalarials. Increased parasite burdens and reduced host immunity, both of which occur with HIV infection, are associated with increased failure rates.[22,23]

### Non-falciparum malaria, malaria in returning travellers, and Odyssean malaria

In sub-Saharan Africa, between 5% and 10% of malaria infections are caused by the other Plasmodium species, namely *P. vivax*, *P. ovale* and *P. malariae*. *P. vivax* is a parasite of both tropical and temperate climates, and accounts for the majority of malaria in Central America, the Middle East and Oceania. In West Africans, who lack the Duffy blood group, *P. vivax* malaria is absent. The core area for *P. ovale* is tropical Africa, and a separate focus is well established in Southeast Asia. Little is known of the extent of non-falciparum malaria in South Africa. Malaria in returning travellers is an increasing and significant problem. A recent study in this group in Gauteng province has shown a significant delay in presentation to health practitioners, a higher mortality than in the traditional transmission malaria areas with established malaria control programmes, and a definite need for health promotion to advise travellers on prevention of malaria (I Weber, personal communication). Forty-six cases of Odyssean malaria were identified in Gauteng province over the period 1996 - 2004. These most likely resulted from infection transmitted by mosquitoes imported in various forms of transport including suitcases, mini-buses and aeroplanes. Factors contributing to delay in diagnosis and high mortality in this group are the nonspecific nature of malaria, which can mimic *inter alia* septicaemia, viral hepatitis and influenza; the absence of a history of travel; and automated routine laboratory testing that is not designed to detect parasites.[24]

## Conclusion

The ultimate goal of malaria vaccine research is an effective, affordable vaccine against *P. falciparum*. There are major immunological problems to overcome. The immediate requirement is discovering how to induce strong, non-strain-specific, durable immune responses; to identify protective antigens for stage-specific immunity; and to combine immunogens successfully. Some recent small-scale clinical trials have shown progress towards reaching these goals.[26] Despite successes in malaria control in South Africa, many challenges remain. Importation of malaria cases, the potential for ongoing antimalarial drug resistance, vector insecticide resistance, a large HIV epidemic, and a struggling health service, leave no room for complacency.

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