Centre for Opportunistic, Tropical and Hospital Infections
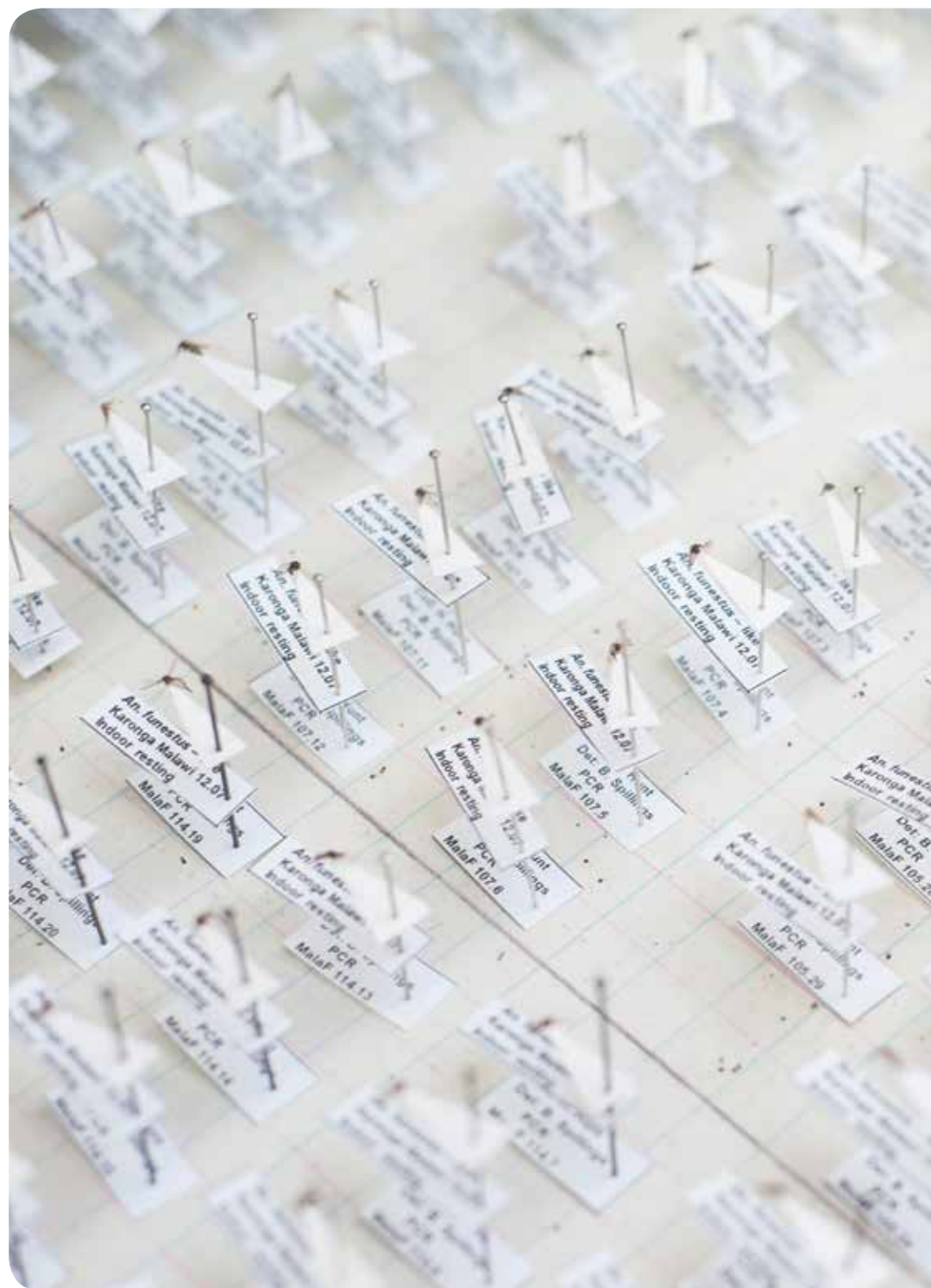
Malaria

CONTENTS

INTRODUCTION
PROF. LUCILLE BLUMBERG

Deputy Director, NICD; Chairperson, South African Malaria Elimination Committee

In the world each year, more than 200 million acute malaria episodes occur, and about 438 000 people, mainly in sub-Saharan Africa, die because of malaria. There is presently renewed interest in the possibility of substantially improved control of malaria or even elimination of malaria in some regions, including South Africa. This is possible because of the widespread introduction of more effective malaria treatment, namely, artemisinin-based combination therapy (ACT). Improved primary-care level diagnosis through use of rapid malaria tests is another important contribution.

Historically, malaria control in South Africa has relied mainly on indoor residual insecticide spraying (IRS) of houses. Its success depends on the assumption that the vectors bite humans indoors then rest on the walls. *Anopheles arabiensis*, an important vector in southern Africa, with its wider range of behaviours, can be controlled but not eliminated with residual spraying of houses. Elsewhere, in countries with high malaria transmission insecticide-impregnated bednets have had significant impact. Another hope for malaria control in highly endemic areas has been sparked by the recent moderate successes of the RTS,S/AS02 malaria vaccine phase 3 trials. The duration of protection may, however, be limited. While a vaccine may ultimately be the only long-term hope for malaria control, achieving prolonged high-level protection through vaccination against malaria is clearly a difficult goal.

Compared with most of sub-Saharan Africa, South Africa is fortunate in several ways regarding malaria: it is at the southern extreme of malaria distribution on the continent, and relatively small areas experience seasonal transmission; it has a well-organised national malaria control programme; and a relatively well-developed scientific, economic and health infrastructure. However, with importation of malaria cases from neighbouring countries, antimalarial drug resistance, vector insecticide resistance, climatic events, other major public health problems such as HIV and tuberculosis, and challenges to preventive and curative health services, there are no grounds for complacency about malaria in South Africa.

Success in elimination can work against itself: as numbers of cases drop, malaria is seen as less of a priority, and therefore health budgets may be re-assigned elsewhere. In addition, fewer cases mean less clinical experience is gained in managing patients, and without a substantial awareness and educational thrust, mortality rates for this treacherous disease are bound to increase.

South Africa and its neighbours need to understand that, notwithstanding recent successes in controlling malaria, only a massive collective effort will eliminate malaria in the region.

WHAT IS
MALARIA?

Malaria is a disease caused by single-celled parasites that have a life cycle requiring 2 hosts – a mosquito vector, and a vertebrate host. There are many different animal, bird, and reptile malarias, but it is human malaria as a clinical and public health problem that is of primary concern.

Malaria has been associated with human morbidity and mortality for countless centuries, with the first reports of human malaria infections appearing in Chinese medical texts dating as far back as 2700 BC. Initially it was thought the air around salt marshes played a role in the spread of the disease, giving rise to the name malaria, which is derived from two Italian words 'mal' (bad) and 'aria' (air). Despite the long association between humans and malaria, the causative *Plasmodium* parasites were only identified in 1880 when a doctor examined the blood of a malaria patient and observed them. It took a further 17 years before the role played by mosquitoes in malaria transmission was finally elucidated.

Over the course of history malaria has infected and killed millions of individuals, and decimated armies, populations, countries and economies. Fame and fortune provides minimal protection from malaria, with many well-known personalities past

Anopheles mosquito

and present, including Genghis Khan, Tutankhamun, John F. Kennedy, David Livingstone, Louis Trichardt, Mother Teresa, Michael Essien, Jane Goodall, Didier Drogba and Wilson Kipketer, having been infected with malaria. Although malaria is currently a preventable and treatable disease, it remains a major contributor to human morbidity and mortality in most of the developing world, with Africa particularly severely ravaged by the disease.

KEY MALARIA
FACTS

- Malaria is a preventable, treatable disease

- Malaria vector mosquitoes generally bite between dusk and dawn

- Only certain anopheline mosquitoes can transmit malaria

- Half of the world's population is at risk of malaria

- In 2015 there were approximately 214 million malaria cases and 438 000 malaria fatalities

- Over 80% of the cases and 90% of the fatalities occur in Africa

- One child dies every minute from malaria in Africa

- Malaria immunity is rapidly lost in the absence of exposure to malaria

- Non-immune travellers are at high risk for severe malaria

- Early diagnosis and prompt treatment reduces severe disease and death

- When travelling to high risk areas prophylaxis and/or personal protection measures are recommended

- Indoor residual spraying for vector control is the most effective way to rapidly reduce malaria transmission

- Emergence of antimalarial drug and insecticide resistance threatens control and elimination efforts

1/2 of the **WORLD'S population is at risk of MALARIA**

EVERY **Seconds** **60** 1 CHILD dies of MALARIA in Africa

EARLY Diagnosis & prompt TREATMENT reduces severe MALARIA
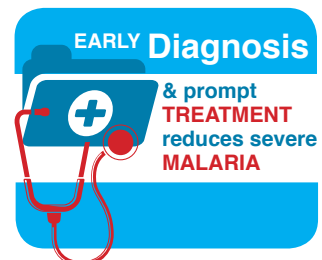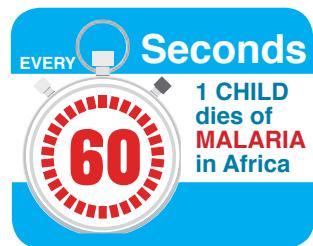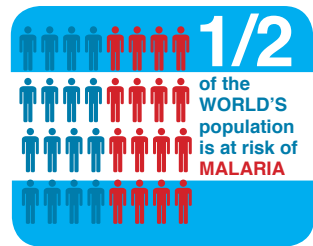
THE PROBLEMATIC
PLASMODIUM PARASITES!
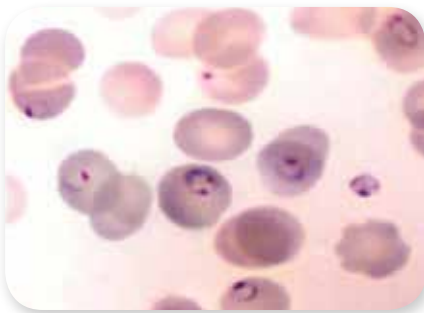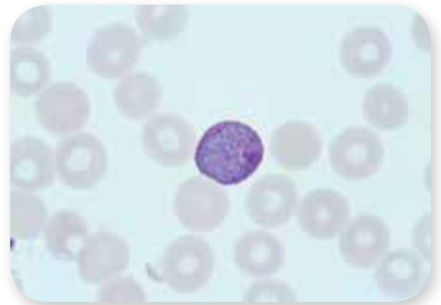

P. falciparum

P. vivax

Parasites of five different *Plasmodium* species (*P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi*) are responsible for human malaria infections. The most virulent, *P. falciparum,* is unfortunately also the most prevalent in Africa. This parasite species multiplies rapidly, invading and destoying red blood cells, causing severe anaemia. If left untreated the infection generally progresses to severe malaria, which often is fatal as it is associated with central nervous system shut-down and major organ failure.

While *P. vivax* infections are generally less virulent than *P. falciparum* infections, complications with *P. vivax* infections occasionally occur, and include splenomegaly and splenic rupture.

Plasmodium vivax parasites have the widest geographic distribution of all the human malaria species and, together with *P. ovale* infections, are associated with relapsing (recurring) malaria. Both these parasite species have hypnozoites, dormant parasite liver stages, which, after the initial infection has cleared from the blood stream, activate and enter the blood, causing another malaria infection.

THE FIFTH HUMAN
MALARIA PARASITE

In 2010 *Plasmodium knowlesi,* a monkey malaria parasite, was recognised as the fifth human malaria parasite species following the discovery of people in Malaysia that were infected with *P. knowlesi* parasites. It is unusual for malaria parasites to cross species barriers. At present, human *P. knowlesi* infections have only been reported from areas in Malaysia and other southeast Asian countries, where humans and monkeys sometimes live in extremely close proximity. Under a microscope *P. knowlesi* parasites are often misidentified as *P. malariae*, as the two species look very similar. However, unlike *P. malariae* infections, *P. knowlesi* infections can be highly lethal as the parasites reproduce every 24 hours, reaching very high parasite loads at an alarming rate.
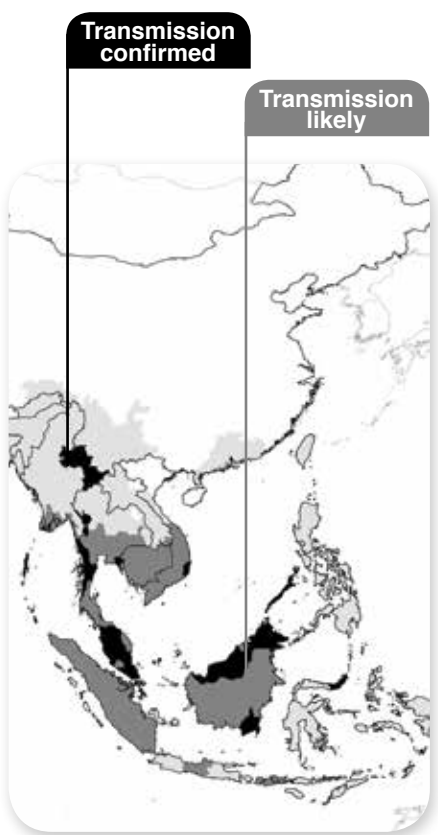

Long-tailed macaques

Transmission confirmed

Transmission likely
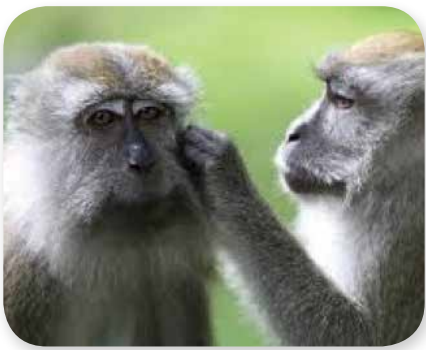
Distribution of *P. knowlesi* in South East Asia

Source: Moyes CI, *et al.* (2014) Defining the geographic range of the *Plasmodium knowlesi* reservoir. PLoS Negl Trop Dis 8(3):e2780

'THE FEMALE OF THE SPECIES IS MORE DEADLY THAN THE MALE!' (Rudyard Kipling 1865-1936)

No statement more aptly describes female *Anopheles* mosquitoes associated with malaria transmission. As male *Anopheles* mosquitoes do not blood feed, they play no direct role in the malaria transmission cycle. Only about 60 of the approximately 460 recognised *Anopheles* species have been implicated in malaria transmission. Classification as a potential vector mosquito is dependent upon two factors: first, females requiring and taking blood meals from vertebrates, and secondly, the mosquito immune system allowing malaria parasites, ingested with the blood meal, to complete their life cycle while in the mosquito, eventually being carried in her saliva when she bites another victim.

At least ten different *Anopheles* species have been identified as vectors of human malaria in Africa. Their efficiency as malaria vectors and contribution to the continent's malaria burden varies considerably and is determined by their level of interaction with humans, their geographic distribution and their physiological characteristics. Africa's high malaria burden can partially be attributed to the region-wide distribution of the three most efficient *P. falciparum* malaria vectors, namely *An. gambiae*, *An. arabiensis* and *An. funestus*.

Head of *Anopheles funestus*

Adult *Anopheles* female
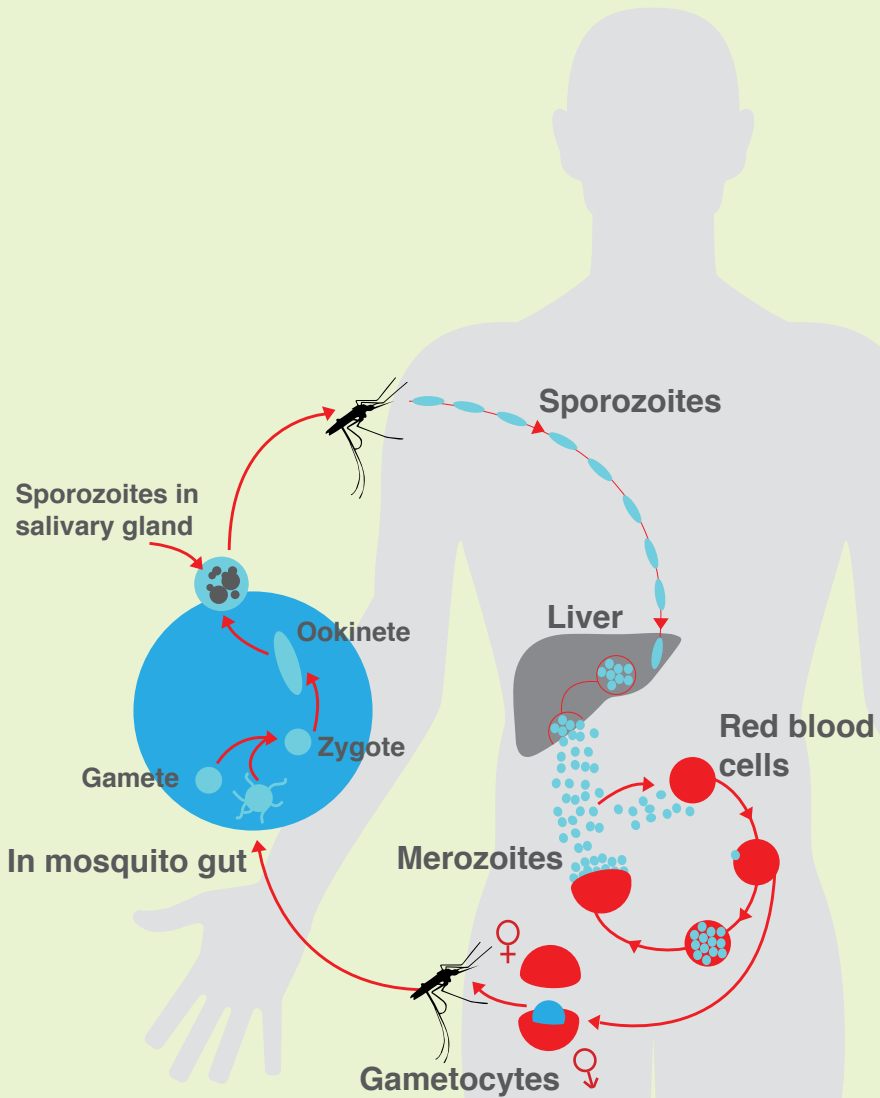
THE MALARIA
LIFE CYCLE

Malaria parasites have a complex life cycle requiring two different hosts for the successful generation of the next set of infective parasites.

The malaria parasite life cycle consists of 5 distinct stages:

1. Infective stage: Sporozoites are injected into the blood stream by a mosquito during blood feeding.
2. Liver stage: Within 30 minutes the sporozoites enter the liver and invade the liver cells (hepatocytes) where they multiply asexually to produce many merozoites. This asexual division continues for 7-30 days (depending on parasite species) before the merozoites are released from the liver cells into the blood stream. No signs or symptoms are exhibited during this stage, called the 'incubation period'. For falciparum malaria, this is usually 10 to 14 days after infection. Other species generally have variably longer incubation periods. Relapsing malaria species *(P. vivax, P. ovale)* have dormant liver stages called hypnozoites. These reactivate at variable times to cause relapses.
3. Blood stage: Once in the blood stream, merozoites invade red blood cells (erythrocytes) where they undergo further asexual multiplication. Infected blood cells eventually burst open freeing the young merozoites to invade other uninfected red blood cells. This process is repeated while the patient lives, inducing malaria signs/symptoms as cellular debris and parasite by-products are released into the blood stream. Some merozoites develop into the sexual parasite form, the gametocytes.
4. Reproductive/gametocyte stage: Male and female gametocytes circulating in the peripheral blood are taken up while a female mosquito is feeding. Inside the mosquito gut male and female gametes fuse to form motile zygotes called ookinetes. These ookinetes then penetrate the mosquito gut wall forming oocysts.
5. Sporogony: Another phase of division occurs in the oocysts forming sporozoites. These sporozoites migrate to the mosquito salivary glands, ready for inoculation into a human host when the female mosquito takes her next blood meal.

The Malaria Life Cycle

Sporozoites

Sporozoites in salivary gland

Ookinete

Zygote

Gamete

In mosquito gut

Liver

Red blood cells

Merozoites

Gametocytes ♀ ♂

SIGNS AND SYMPTOMS
OF MALARIA

As the signs and symptoms of malaria are initially non-specific, it is recommended that anyone with a 'flu-like illness (see table below) after visiting a malaria risk area, irrespective of malaria season, transmission intensity or chemoprophylaxis use, be tested for malaria by blood smear or rapid diagnostic test.

| Uncomplicated malaria	Severe (complicated) malaria
Fever (>37.5 ˚C)	Impaired consciousness
Headaches	Inability to sit or stand up straight
Rigors (cold shivers/hot sweats)	Multiple convulsions
Arthralgia/myalgia (joint/muscle pains)	Respiratory distress
Diarrhoea, nausea and vomiting	Circulatory collapse
Loss of appetite; inability to feed in babies	Jaundice
Dizziness, sore throat	Pulmonary oedema
Muscle weakness and lethargy, particularly in young children	Acute respiratory distress syndrome (ARDS)
	Haemoglobinuria

HIGH RISK
GROUPS

Young children
(under the age of 5)

Pregnant women

Immunocompromised
patients (patients
undergoing
chemotherapy,
HIV patients)
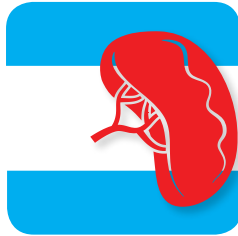
Splenetomised
individuals (spleen
removed for various
reasons)

The elderly

Non-immune
individuals

MALARIA TREATMENT
AND PREVENTION

Early diagnosis and treatment of malaria reduces disease and prevents deaths. It also contributes to reducing malaria transmission.

Fingerprick blood collection

Blood smear preparation

The best available treatment, particularly for *P. falciparum* malaria, is artemisinin-based combination therapy (ACT). All cases of suspected malaria should be confirmed using parasite-based diagnostic testing (either microscopy or rapid diagnostic test) before administering treatment. Results of parasitological confirmation can be available in 15 minutes or less.

Vector control is the main way to reduce malaria transmission at the community level. It is the only intervention that can reduce malaria transmission from very high levels to close to zero. For individuals, personal protection against mosquito bites represents the first line of defence for malaria prevention. In many high-transmission areas, long-lasting insecticidal nets (LLINs) are used. In South

Africa, with relatively low levels of malaria, community malaria control depends on indoor spraying with residual insecticides. Bednets, mosquito repellents applied to the skin, as well as the use of window and door screens, anti-mosquito coils or sprays, can reduce the risk of malaria.

Antimalarial medicines can also be used to prevent malaria. For travellers, malaria can be prevented through chemoprophylaxis, which suppresses the blood stage of malaria infections, thereby preventing malaria disease.

Rapid diagnostic tests

Malaria diagnosis

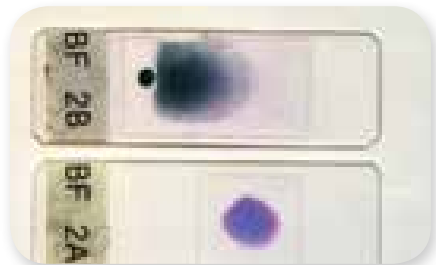The traditional method, which is still widely used, is microscopic examination of stained blood films. More modern methods include rapid diagnostic tests, and molecular techniques. All diagnostic tests have advantages and disadvantages, and their use must be tailored for particular circumstances.
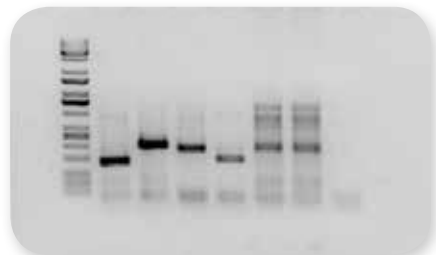

Unstained blood smear

Stained blood smears

Blood smear microscopy

Malaria PCR gel

13

GLOBAL MALARIA
DISTRIBUTION

Bioinformatics data suggest P. falciparum *parasites originated in Africa and radiated outwards to the new world during the migration of people from the old world. In the early 1900s malaria was extremely prevalent across the globe, occurring on every continent except Antarctica.*

As malaria control interventions became more effective, particularly following the discovery of the anti-mosquito properties of DDT (dichloro-diphenyl-trichloroethane), a marked decline in malaria cases was noted. This decrease sparked global optimism over the possible eradication of malaria and prompted the WHO to roll out a global malaria eradication campaign in the 1950s. Despite being marketed as a global initiative, the programme excluded Africa, as the continent's high malaria transmission intensity was viewed as a major obstacle to the eradication efforts. Nonetheless, the campaign was extremely effective in both Europe and America, where malaria was effectively eradicated following the campaign. Unfortunately the same could not be said for Asia, as malaria cases rapidly rebounded after eradication-related activities were suspended.

Concerted efforts to control and/or eradicate malaria ceased following the partially-successful 1950s malaria eradication campaign. In the 60 or so years that followed malaria continued to be a major cause of human suffering in most of the developing world, with Africa bearing the brunt of the disease. It was only in the early 2000s that controlling malaria, particularly in Africa, became a priority, largely thanks to funding from numerous international non-governmental organisations.

Despite the sustained implementation of effective interventions, more than half the world's population remains at risk of malaria. According to the 2015 WHO World Malaria Report, Africa accounted for majority of the 214 million cases and 90% of the estimated 438 000 malaria-related fatalities, most of which were children under the age of 5.

Malaria
FREE

1900

1946

1965

1975

1994

2002
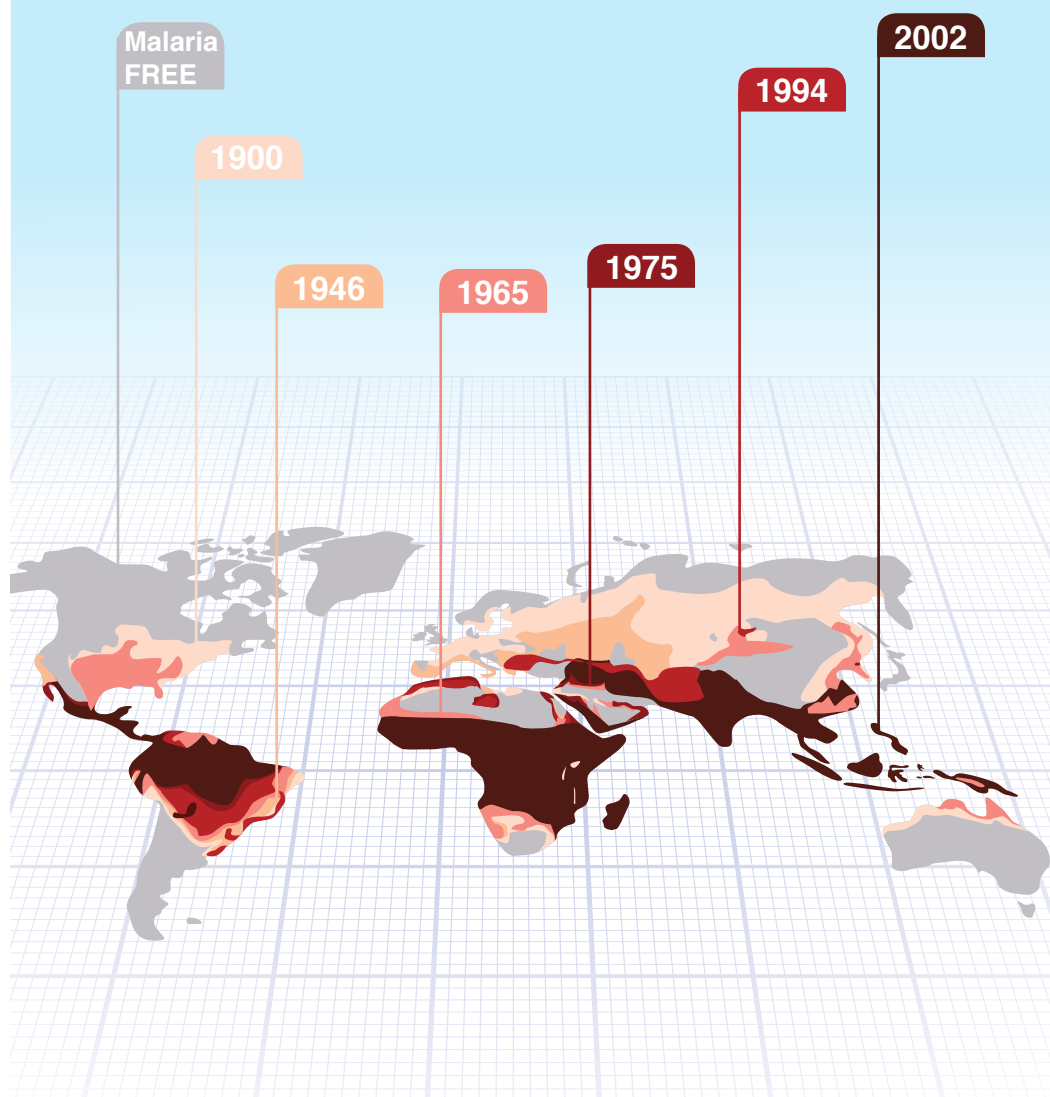
Changes in extent of malaria during the 20th and 21st centuries.
Source: Hay *et al.,* (2004) The global distribution and population at risk of malaria: past, present, and future. Lancet Infectious Diseases. 4(6):327-36.

MALARIA AND AFRICA
– THE PERFECT MATCH

Most of sub-Saharan Africa unfortunately has the ideal environmental and socio-economic conditions for sustained malaria transmission.

The main factors include:

- Favourable climatic conditions for vector mosquito growth and development

- Constrained health infrastructure and systems, particularly in the malaria affected areas

- Lack of adequate funds for the sustained implementation of effective interventions

- High level of poverty amongst most of Africa's rural population, limiting access to adequate health care

- High prevalence of insecticide and antimalarial drug resistance

- Uncontrolled, unregulated access to antimalarials in many African countries

- Easy access to counterfeit antimalarials, which contributes to the emergence of drug-resistant parasites

- High prevalence of HIV that has negatively impacted malaria control efforts

- High levels of civil unrest forcing mass migration

- Frequent mass movement of populations across borders

Very high malaria endemicity

High malaria endemicity

Low malaria endemicity

Moderate malaria endemicity
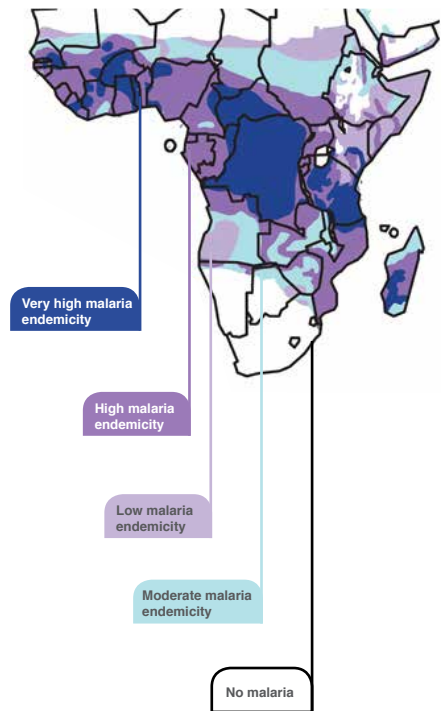
No malaria

MALARIA IN
SOUTH AFRICA

Prior to the introduction of malaria control measures, malaria was widespread in South Africa, occurring in what are now the provinces of Limpopo, Mpumalanga, KwaZulu-Natal as far south as Durban, and northern Gauteng down to Pretoria. During the early 1900s malaria epidemics were a common occurrence, particularly in KwaZulu-Natal, where over 4 000 cases and 42 deaths were reported during the 1904/1905 epidemic.

Entomological investigations identified *An. gambiae* complex as the vector species, while microscopic examination of patient blood smears revealed initial infections were due to *P. vivax* (or, more likely, *P. ovale*) with *P. falciparum* infections becoming more common as the outbreak progressed. Intense larvicidal measures together with case management using quinine initially kept malaria at bay.

Trapping of indoor resting mosquitoes

Malaria in South Africa, 1938

RHODESIA

BECHUANALAND

LORENZO MARQUES

Pretoria

Lorenzo Marques

Swaziland

Serious risk in summer

Continued high risk

Moderate risk in summer

Epidemic, slight risk

Durban

17
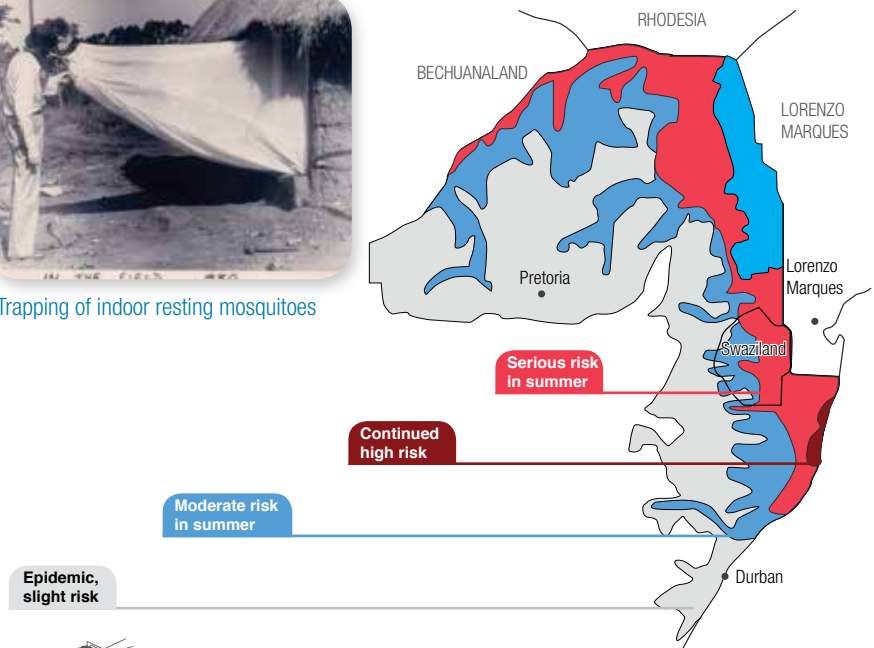
Malaria in South Africa, 1971-2013

Mosquito surveys during the 1920s, first around military hospitals and then more extensively across South Africa, confirmed the wide distribution of efficient malaria vectors. This prompted researchers from the South African Institute for Medical Research (SAIMR) to develop innovative methods to control vector mosquitoes. The discovery by SAIMR researchers that pyrethrum had insecti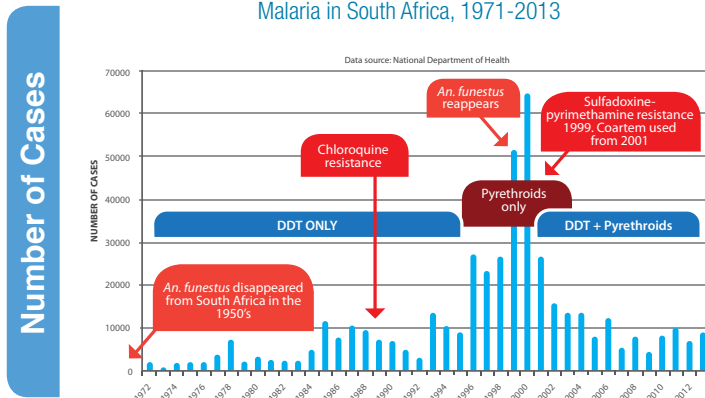cidal properties, and that female *An. funestus* preferentially rest inside human dwellings following the acquisition of a blood meal, gave rise to the idea of spraying the inner walls of dwellings as a means of vector control.

Field experiments in Limpopo and KwaZulu-Natal conclusively demonstrated a dramatic decline in malaria transmission following regular indoor residual spraying (IRS) with pyrethrum. Further support for this technique was provided when the 1930-1933 malaria epidemics in KwaZulu-Natal were brought under control using insecticide spraying. These findings led to the establishment of insecticide-based indoor spraying programmes in South Africa and many other malaria endemic countries. Interestingly, indoor spraying using DDT was the core intervention utilized during the global malaria eradiation campaign. Stringent implementation of indoor spraying using DDT resulted in the eradication of *An. funestus* from South Africa and ensured

malaria epidemics were rare until the mid-1980s. A marked increase in chloroquine-resistant *P. falciparum* parasites caused a sharp increase in malaria cases, forcing a drug policy change from chloroquine to sulfadoxine-pyrimethamine (SP). Thereafter malaria case numbers declined to baseline levels only to begin rising again during the mid-1990s, peaking at over 60 000 cases during the 1999/2000 malaria season (see figure above).

Three major factors contributed to this major epidemic:
a) favourable climatic conditions,
b) the reappearance of pyrethroid-resistant *An. funestus* and
c) the emergence of SP-resistant *P. falciparum* parasites.

The reintroduction of DDT for IRS activities together with the replacement of SP with the artemisinin-based combination therapy, artemether-lumefantrine (Coartem), dramatically reduced malaria transmission.

The sustained implementation of these effective malaria control measures has effectively pushed back the malaria distribution to low-lying border regions, allowing South Africa to embark on the ambitious goal of eliminating malaria within its borders by 2018.

CURRENT MALARIA RISK
IN SOUTH AFRICA
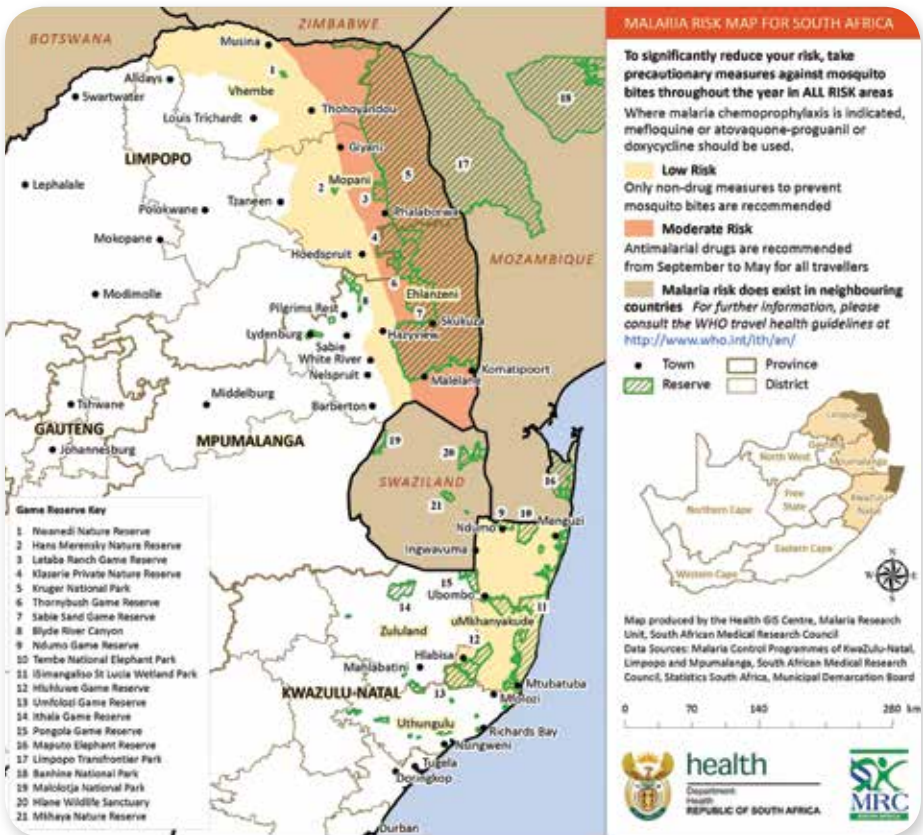
MALARIA SURVEILLANCE AND OPERATIONAL **RESEARCH AT THE NICD**

The Vector Control Reference Laboratory (VCRL) was originally established in 1924 to investigate vector-borne diseases affecting gold mine workers and now primarily focuses on malaria vector biology and control.

One of the core VCRL functions is to provide support to the National and Provincial Departments of Health Malaria Control Programmes by:

- Conducting training of postgraduate students and Department of Health personnel via research and a range of short-term training courses

- Identification of malaria vector species and vector incrimination

- Characterising insecticide resistance mechanisms and factors that affect resistance expression

- Conducting operational research in malaria affected regions

- Offering expert advice on malaria elimination and specific vector control activities

- Conducting field work to support vector control and surveillance activities

- Production of malaria vector distribution maps

- Offering technical support to provincial malaria control teams

- Evaluating alternative methods of vector control

- Evaluating the efficacy of novel vector control products

The VCRL maintains the third-largest reference collection of African arthropods of medical importance in the world, and houses live cultures of members from both the *An. gambiae* complex and *An. funestus* group, many of which are major malaria vector species. The cultures and reference collection provide a unique resource for research and teaching purposes. All VCRL staff and students are also affiliated to the Wits Research Institute for Malaria (WRIM) at the University of the Witwatersrand.

Human landing catches

Emptying window traps

Looking for mosquitoes

MONITORING INSECTICIDE RESISTANCE IN
SOUTHERN AFRICA

Adult female *An. funestus* mosquitoes are almost entirely endophilic (indoor-resting), making them extremely susceptible to control by indoor spraying of residual insecticides (IRS). However the development of insecticide resistance has the potential to cause severe epidemics, as seen in South Africa during the 1999/2000 malaria season. Researchers from the VCRL demonstrated that the emergence of pyrethroid- and carbamate-resistant *An. funestus* populations in both South Africa and Mozambique contributed significantly to the sharp increase in malaria cases and fatalities. Fortunately, the same researchers showed the *An. funestus* populations to be fully susceptible to DDT, prompting the South African government to reintroduce DDT for IRS operations in conjunction with pyrethroids in 2000, effectively halting the epidemic.

Ongoing research at the VCRL has revealed that the pyrethroid resistance in *An. funestus* adults is associated with the over-production of certain monooxygenase detoxification enzymes as well as cuticular thickening, which reduces the rate of insecticide penetration. Increased production of glutathione-S-transferase (GST) has also been shown to protect mosquitoes from oxidative damage caused by insecticide exposure.

In order to manage insecticide resistance in target populations it is not only important to understand the mechanism/s of resistance, but also how resistance is inherited and whether or not any fitness costs are incurred by individuals carrying resistance genes. A VCRL study showed that pyrethroid resistance in an *An. funestus* laboratory strain originating from southern Mozambique does not cause any loss of fitness, implying that the removal of insecticide selection pressure will not necessarily result in the loss of the resistant phenotype. This phenotypic stability may account for the extremely rapid spread of this resistance phenotype through Mozambique and into Malawi.

Insecticide spray pumps

Data from the VCRL have also revealed that South African *An. arabiensis* have developed resistance to both pyrethroid insecticides and DDT. Studies at the VCRL have established that the resistance profile is based on the up-regulation of certain P450 genes, redox genes and GSTs. The occurrence of two major malaria vector species in South Africa with differing insecticide resistance profiles has necessitated the development of resistance management strategies aimed at maintaining effective malaria vector control activities in the affected provinces.

The VCRL remains dedicated to providing the necessary operational research and surveillance to support South Africa's malaria elimination agenda. To this end, the VCRL is involved in evaluating alternative methods of malaria vector control, such as the sterile insect technique.

Collecting knocked-down mosquitoes

Searching for mosquito larvae

Searching for mosquitoes in a traditional home

STERILE INSECT
TECHNIQUE

Outdoor mosquito cages for
SIT experiments

Releasing sterile mosquitoes into the
outdoor cages

The sterile insect technique (SIT) is based on the principle of suppressing a target insect population by mass rearing males, sterilising them and then releasing them into a target pest/vector population. If successful, mating between sterilised males and wild females will not result in the production of offspring, leading to population suppression.

There are important reasons why SIT should be considered for inclusion in existing malaria control and elimination programmes. The continued incidence of insecticide resistance in malaria vectors is a major concern and the addition of non-chemical methods of control to the anti-malaria armoury is therefore desirable. SIT also has the advantage of reducing the use of insecticides, which is of concern in terms of environmental protection.

The main objective of the SIT project co-ordinated by the VCRL is to ascertain whether it is feasible to use mosquito colonies held in South African facilities to field SIT programmes for malaria vector control. Baseline data collections in northern KwaZulu-Natal have produced valuable biological information on the target species, *An. arabiensis*. Funding for this project is via the International Atomic Energy Agency, the Industrial Development Corporation and the South African Nuclear Energy Corporation (NECSA) through its Nuclear Technologies in Medicine Biosciences Initiative (NTeMBI) – a national platform funded by the Department of Science and Technology.

TRACKING ANTIMALARIAL
DRUG RESISTANCE

The rapid spread and establishment of parasites resistant to the antimalarials of choice played a leading role in last the two major South African malaria epidemics. In an effort to ensure that effective antimalarials are in place, the WHO recommends regular drug efficacy monitoring by clinical trials or routine surveillance for validated molecular markers of antimalarial drug resistance. This regular monitoring has become even more important following confirmation of artemisinin-resistant parasites in South East Asia, the historic epi-centre of both chloroquine and sulfadoxine-pyrimethamine drug resistance. Acknowledging the importance of this routine surveillance, the NICD in collaboration with the Department of Health and Provincial Malaria control programmes established a malaria surveillance programme in 2015 to monitor the prevalence of antimalarial drug resistance markers in parasite isolates from the malaria-endemic regions of South Africa. Samples (whole blood, finger-prick dried blood spots or malaria-positive RDTs) collected at health facilities in Limpopo, Mpumalanga and KwaZulu-Natal will be assessed for the presence of well-established and novel molecular markers of antimalarial drug resistance. It is envisaged this surveillance will facilitate the early detection of emerging resistance, allowing for a timeous drug policy change, thereby preventing a drug-resistant malaria outbreak.

Blood spots

Punching out blood spots for analysis

# ON THE ROAD TO MALARIA ELIMINATION **- DETECTING EVERY MALARIA CARRIER**

As South Africa transitions from malaria control to malaria elimination, intervention focus shifts from reducing malaria case numbers to halting onward malaria transmission. To achieve this every malaria carrier must be detected and successfully treated.

However, detecting every malaria carrier is confounded by a number of factors, the two most concerning being asymptomatic carriers (individuals infected with malaria but who display no signs and symptoms of malaria), and carriers of sub-microscopic malaria infections (patients with parasite loads below the detection limits of both microscopy and RDTs).

As the momentum to eliminate malaria grows, novel, more sensitive technologies aimed at achieving this goal are continually being produced. One such technology, LAMP (loop-mediated isothermal amplification), is currently being tested as a point-of-care device capable of rapidly detecting extremely low parasitaemias in rural settings, enabling prompt diagnosis and treatment. Initial laboratory evaluations by the Parasitology Reference Laboratory have shown LAMP to be sensitive and extremely user-friendly. During the upcoming malaria season the ability of LAMP to detect asymptomatic and/or sub-microscopic infections at select rural health facilities within the malaria-endemic provinces will be assessed. Data obtained will be used to inform a LAMP diagnostics policy for the malaria-endemic provinces.
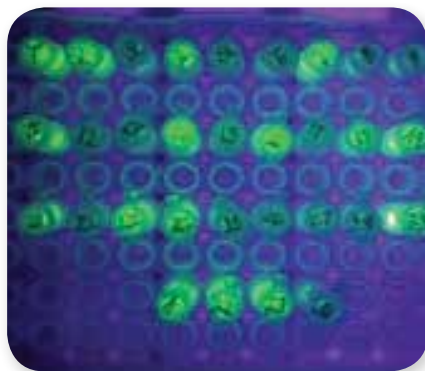
Fluorescent green samples are malaria positive by LAMP

ODYSSEAN
MALARIA

Searching for mosquitoes

Collecting mosquitoes

Transmission of malaria outside endemic areas is inherently unexpected, which delays diagnosis and treatment, and is therefore frequently associated with severe illness or a fatal outcome. The recognition in the 1970s in Europe of such cases of 'airport malaria' (and the related suitcase, baggage or luggage malaria) led to the awareness that aircraft are not the only vehicles that can transport vector mosquitoes out of their normal habitats, and the entities of harbour, container, and minibus (or taxi rank) malaria were described. We coined the term 'odyssean malaria' to unify all these various modes of transport used by malaria vectors. Odysseus was the legendary Greek hero who, on his way home from the Trojan wars, wandered the Mediterranean region, experiencing many adventures and narrow escapes. Similarly, a lost mosquito might

have many dangerous encounters as she navigates a suitcase, aircraft cabin, cargo hold or taxi, escaping being deliberately swatted, accidentally squashed, eaten by a predator, or succumbing to heat or cold on her way to her next blood meal, far from her natural home.

Between 1996 and 2015, we have accumulated more than 80 cases of odyssean malaria in Gauteng, and one in the Western Cape. We believe that most, if not all, result from mosquitoes hitching rides from endemic areas on minibus taxis, trucks, and cars. These cases have a much higher mortality compared with the national malaria case fatality rate, and always attract intense local media interest and speculation about spread of malaria to this (non-endemic) province. In partnership

with the provincial Departments of Health, we investigate the circumstances of the cases to exclude mechanical transmission (via blood transfusions or needlesticks) and to check for vector mosquitoes in patients' houses, and more importantly, to look for local breeding sites of vector mosquitoes.

While the climatic conditions on the Witwatersrand are not suitable for prolonged vector breeding, during spells of warm weather local breeding could happen, with a risk for local epidemics. In recent malaria seasons nearly 20 odyssean malaria cases were investigated.

Searching for breeding sites

Searching for mosquitoes

CENTRE MALARIA-RELATED
ACTIVITIES

- Anopheline species identification and malaria vector incrimination for the provincial malaria control programmes in South Africa and elsewhere

- Laboratory culturing of five African malaria vector species and one closely-related non-vector species

- Scientific and operational support for entomological surveillance and malaria vector control at national and regional levels

- Evaluation of the feasibility of the sterile insect technique for malaria vector control in South Africa

- Odyssean malaria outbreak response in Gauteng

- Assessment of the comparative efficacy of targeted indoor residual spraying for malaria control in South Africa

- Detection and characterisation of insecticide resistance in malaria vector populations in South Africa, Zimbabwe, Zambia and Mozambique

- Evaluation of the efficacy of novel insecticidal compounds against African malaria vector species

- Evaluation of a range of trapping techniques for field malaria entomology surveillance in South Africa

- Assessment of aestivation as an over-wintering strategy in the major malaria vector *Anopheles arabiensis* in South Africa

- Development of a host-parasite interactions research facility via the Mosquito-Parasite Infection Resource Centre (MIRC)

CENTRE MALARIA-RELATED
ACTIVITIES

- Identification and characterization of a candidate mosquito protective antigen, akirin, for the control of African malaria vector species
-
- Understanding population structuring, physiological stress responses, biochemical interactions and phenotypes of epidemiological significance in African malaria vectors

- Establishing and evaluating methods for antimalarial resistance surveillance, including artemisinin resistance

- Evaluating rapid diagnostic test quality and performance for national diagnostic, control and surveillance programme procurement

- Monitoring in-use accuracy of rapid diagnostic tests

- Evaluating performance of nucleic acid-based tests for malaria e.g. loop-mediated amplification (LAMP), and polymerase chain reaction (PCR) methods

- Provision of laboratory quality guidelines for the provincial malaria control programmes and the National Health Laboratory Service

- Provision of national reference laboratory function guidelines for the SADC region

- Provision of malaria reference diagnostic services and external quality assessment programmes in sub-Saharan African countries, and supporting the South African National Health Laboratory Service EQA programme for malaria and other blood parasites

- Education of trainee and qualified pathologists, scientists, and technical staff in the theory and practice of malaria diagnosis, surveillance, and control

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NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Centre for Opportunistic, Tropical
and Hospital Infections (COTHI)

Tel: (011) 386-6000
Fax: (011) 386-6620

Modderfontein Road
Sandringham, Johannesburg
South Africa

www.nicd.ac.za

Wits Research Institute for Malaria
Faculty of Health Sciences
7 York Road
Parktown
Johannesburg 2001