THE PATHCARE NEWS

MALARIA – AN ONGOING HEALTH PROBLEM

Malaria is a serious infectious disease caused by Plasmodium parasites, primarily transmitted through the bite of an infected female Anopheles mosquito. While *Anopheles* mosquitoes are the primary vectors, not all species of *Anopheles* can transmit the disease, and transmission rates vary based on the species involved. In rare cases, malaria transmission can also occur through blood transfusions, bone marrow transplants, or trans-placentally from mother to foetus.

Epidemiology

Malaria remains a major global health threat, with an estimated 84 countries affected and the burden has since increased in recent years. In regions where malaria is endemic, the disease remains a constant public health challenge. **See fig 1:**

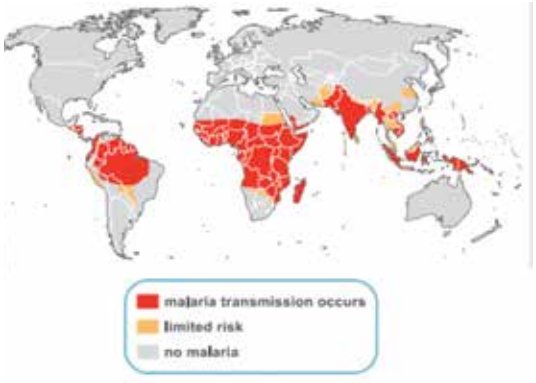


Fig 1: This map shows parts of the world where malaria transmission occurs.

In South Africa, malaria is predominantly transmitted in specific regions along the border areas, including parts of Limpopo, Mpumalanga, and KwaZulu-Natal. The transmission is highly influenced by climatic factors such as temperature, rainfall, and humidity and in SA, transmission tends to be seasonal, with the number of cases rising in October, peaking during the warm months of January and February, and decreasing towards May. **See fig 2:**

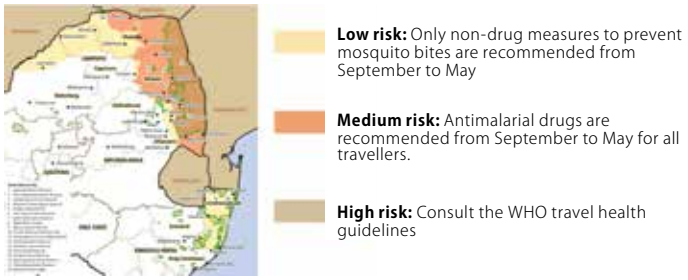


Fig 2: South African Malaria risk Map.

One of the significant contributors to this never ending problem is the emergence of drug resistance, climate variability and resistance to pyrethroid insecticides. These factors further complicate efforts to control the disease.

There are six species of *Plasmodium* that are known to infect humans, each with different geographical distributions and impacts on human health. Of these, *Plasmodium falciparum* and *Plasmodium vivax* are the most significant due to their prevalence and severity. Other species of *Plasmodium* also infect humans, though they are less common or cause less severe disease. **Refer to Table 1:**

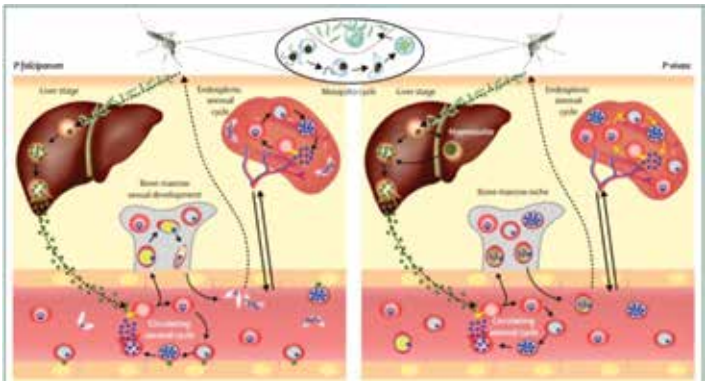
Plasmodium Species	Characteristics	Regions/Distribution	Severity/complications
P. falciparum	Infects RBC of all ages.	Primarily sub-Saharan Africa	Cerebral malaria, organ failure, death if untreated
P. vivax	Invades commonly reticulocytes. Remain dormant in hepatocytes	Asia, South America and parts of the Middle East	Relapsing malaria
P. malariae	Milder forms. Often low parasitaemia	Various regions	Often incidental finding
P. Ovale (curtis + wallikeri)	Milder form of malaria.	Widely distributed geographically	Often incidental finding
P. knowlesi	Primarily infects macaque monkeys, but can infect humans	SE Asia	Severe and fatal in humans, if not treated

Table 1: Characteristics of Plasmodium species

Additionally, there are **seven other zoonotic *Plasmodium* species** that cause geographically restricted human infections. These are even rarer than *P. knowlesi* and generally result in localized outbreaks. While these species are not as widespread, they pose potential challenges in areas where human-wildlife interactions are frequent.

Life cycle of the parasite

When an infected female Anopheles mosquito takes a blood meal, it injects sporozoites (the infectious form of the parasite) into the human bloodstream. These sporozoites enter the hepatocytes, where they multiply and mature. The liver stage of the parasite can last from several days to weeks, depending on the species of Plasmodium. In Plasmodium falciparum and Plasmodium vivax, the parasites undergo a process of asexual multiplication, forming large numbers of merozoites. When the hepatocytes become engorged with merozoites, they rupture, releasing the merozoites into the bloodstream. The merozoites then enter red blood cells (RBCs) where they develop into trophozoite, often referred to as the "ring form" because of its characteristic appearance inside the red blood cell. The trophozoite matures into a schizont, which is a large, multinucleated form of the parasite. The schizont divides and forms numerous new merozoites. The mature schizont ruptures the RBCs, releasing new merozoites into the bloodstream which will then invade fresh RBCs to continue the cycle. The rupture of red blood cells and the subsequent release of merozoites coincide with the abrupt fever and chills commonly associated with malaria. A small proportion of merozoites differentiate into gametocytes. In addition to the bloodstream and liver, asexual stages of Plasmodium falciparum can also be found in the spleen and bone marrow.



The life cycle of Plasmodium parasites is complex, involving both asexual and sexual stages: **Refer to Fig 3:**
Outline of the stages in the life cycle of the Plasmodium parasite.

Pathogenesis of Malaria

The pathogenesis of malaria, particularly in cases of P. falciparum, involves several mechanisms that contribute to the severity of the disease. The clinical manifestations of malaria are largely a result of the interaction between the parasite and the host's immune and vascular systems, leading to organ dysfunction, anaemia, thrombocytopenia, and sometimes death.

In severe cases, a key pathogenic mechanism is **microvascular sequestration.** This occurs when parasitized RBCs cytoadhere to activated and dysfunctional endothelial cells particularly in vital organs like the brain, lungs, kidneys, and placenta. This process leads to obstruction of the microcirculation, impairing blood flow and oxygen delivery to tissues, resulting in ischemia and organ dysfunction.

Anaemia is one of the most common complications of malaria that results because of destruction of parasitized RBCs as well as a significant loss of uninfected red blood cells occurring through oxidative damage, complement-mediated destruction, reduced RBC deformability, increased splenic retention and clearance and dyserythropoiesis. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are particularly vulnerable to oxidative damage, exacerbating anaemia. Additionally, prolonged parasitaemia, delayed presentation to healthcare services and slower parasite clearance also contribute to the worsening of anaemia.

Thrombocytopenia is another common complication in malaria. Like anaemia, it is multifactorial in origin and include platelet consumption, platelet destruction / increased platelet clearance

Diagnostic recommendations

A diagnosis of malaria cannot be confirmed or excluded clinically. Since the clinical presentation is non-specific and may mimic many other diseases, each patient's blood should be examined immediately using a malaria antigen rapid diagnostic test (i.e., RDT) and microscopy of thick and thin Giemsa-stained blood smears to confirm or exclude the diagnosis.

However, in some cases, a negative smear or RDT may not exclude the diagnosis.

If the initial RDT or blood film examination is negative in patients with symptoms compatible with malaria and no other cause can be determined, a series of RDT or blood films should be examined at 6-12 hours intervals. Repeat tests should continue until the diagnosis is confirmed, the patient has recovered, or another definitive diagnosis has been made.

The diagnosis of malaria in itself can be challenging, especially in areas with low parasitemia. Other complementary diagnostic techniques such as immunoroflourscent –based assays (QBC) and Malaria PCR may be employed.

Please note: Malaria is a category 1 notifiable disease, thus must be reported or notified within 24 hours of diagnosis.

The non-specific signs and symptoms of malaria are listed on **fig 4 below:**

Table 2: Outlines all the investigations that are performed by PathCare across the nation, including their limitations.

Signs and Symptoms

Fig 4: Common signs and symptoms of malaria

The time between the mosquito bite and the appearance of symptoms can vary, ranging from 7 to 30 days (in P. falciparum and P. vivax) and even months or years (P. ovale, P. malariae) after the initial infection. This is due to the liver stage of the parasite where it remains dormant.

Severe malaria is characterised by prostration, reduced consciousness, respiratory distress, pulmonary oedema / acute respiratory distress syndrome (ARDS), severe anaemia, hypoglycaemia, shock and jaundice. The severity of the disease is influenced by factors such as the Plasmodium species (most commonly P. Falciparum and P. Knowlesi) the patient's age, pregnancy status, and the timeliness of treatment.

Both heritable and acquired factors modulate the risk of Plasmodium infection and malaria severity. Predisposing factors to malaria include Sickle cell disease, age, malnutrition and obesity, pregnancy HIV, Diabetes and hyposplenism. The protective factors usually include Sickle cell trait, group O individuals, and Haemoglobin C and G6PD deficiency.

Parameters	Microscopy	RDT	QBC	PCR
Principle technique	Morphological interpretation on Giemsa-stained thin and thick smears. Thin smears. Maintains integrity and morphology of RBCs. Thick smears .Involves lysis of the RBCs. Parasites visualised independent of cell structures Gold standard	Ag-Ab binding, display results in the form of visible bands.	Use of capillary tube coated with acridine orange, centrifuging the blood sample and then examining the separated layers under a fluorescent microscope to detected malaria parasites.	DNA amplification by targeting small subunit rRNA/ ssRNA,
Sensitivity	50-100 parasites/ul	50-250paraistes/ul	High	<5 parasite/ul
Specificity	High	Moderate - limited to P.Falc and mixed infections.	High	High
Time consumes	Up to 1h	Within <20min		2- 8 hours
	Quantitative	Qualitative	Qualitative and quantitative	Qualitative and quantitative
Advantages	Inexpensive. Been used for > 100 years, Rapid . Detects other blood parasites (i.e. Trypanosoma, Loa Loa, Babesiosis, etc). Parasite species and stage can be differentiated. Drug induced morphological changes can be observed Screening for other related blood abnormality at once (i.e sickle cells etc). Determination of parasite density. Treatment monitoring.	Simple & Fast. Practical. Can be interpreted by non-expert users. The ones that detect HRP2, an antigen exclusively produced by P. Falciparum,	Can detect low parasite density. Used in treatment monitoring.	Accurate speciation Requiring only a small sample
Limitations	Requires specialized equipment and well-trained staff. Diagnostic errors occur in the setting of low-density parasitaemia (10 – 100 parasites of blood	False positive caused by cross reaction with autoantibodies i.e RF. Can't quantify. Can't detect P. Knowlesi. Not for monitoring of the disease. Limited speciation. Prozone phenomenon (hyperparasitemia/ severe malaria causes exhaustion of antibodies, leading to loss of signal (FN).	Expensive. Shorter stability Skilled personnel	Not easily available. Trained personnel. Test remain positive for weeks after successful treatment. Raised Hct and Hb may produce invalid results. Cross-contamination can produce False +ve results

Microscopy findings: What morphologists see

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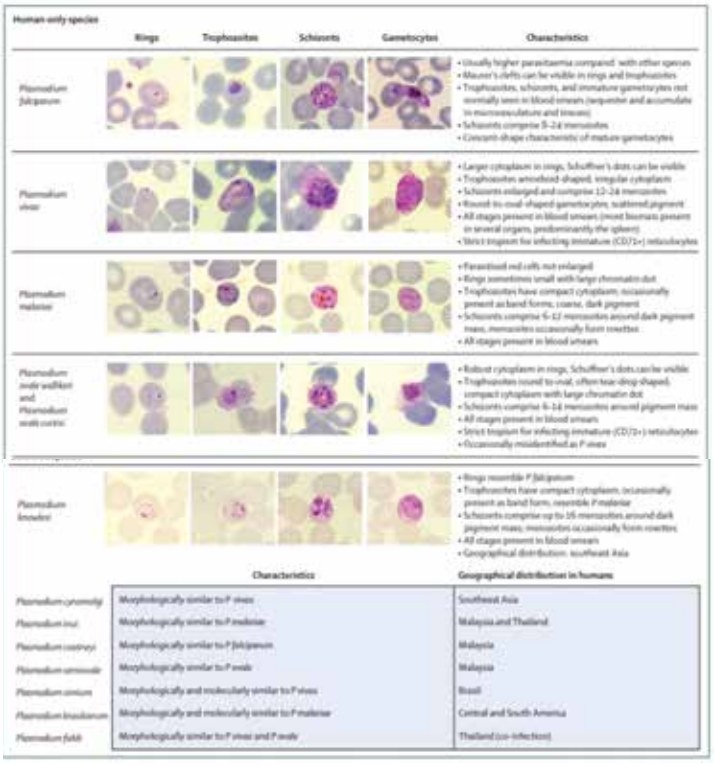


Other diagnostic techniques

There are several advanced diagnostic methods (not routinely performed) for malaria that complement traditional diagnostic approaches including:

ELISA for detecting PfHRP-2, particularly in epidemiological surveys.
Flow cytometry for species identification and quantifying low parasitemia.
Nucleic Acid Amplification Technologies (NAAT), including real-time PCR, for highly sensitive detection, though not suitable for quantifying parasitemia.
LAMP, a promising isothermal method for field use, offering a balance between sensitivity and simplicity.
Point-of-care testing (POCT), which has great potential but faces significant technical challenges.

Advanced techniques like **droplet digital PCR (ddPCR)** and **next-generation sequencing (NGS),** which offer cutting-edge capabilities are currently limited by cost and infrastructure. The key challenge remains to make these advanced technologies more accessible, affordable, and feasible for widespread clinical and field use.

Management

A combination of prevention strategies, early detection, and effective treatment is key to controlling and reducing the burden of the disease. Below are the key components of malaria prevention and treatment, along with some specific guidelines for South Africa.

Prevention of Malaria: The 'ABC' Approach
A: Awareness and Assessment of Malaria Risk - Understanding the malaria risk in different regions is crucial for taking appropriate preventive actions. Travelers to endemic regions should be aware of the risks and take preventive measures.
B: Avoidance of Mosquito Bites - Insecticide-treated nets (ITNs), Indoor residual spraying (IRS), Personal protective measures, and environmental management.
C: Compliance with Chemoprophylaxis (when indicated). This is especially for travellers to malaria-endemic areas. The choice of drug depends on the region visited and the type of *Plasmodium* species prevalent there. Commonly used prophylactic drugs include Atovaquone-proguanil, Doxycycline, and Mefloquine.
D: Early Detection of Malaria Disease.
E: Effective Treatment. South Africa has implemented specific guidelines for malaria treatment and prevention, particularly since malaria is endemic in some regions such as Limpopo, Mpumalanga, and KwaZulu-Natal.

Severe malaria: All patients, regardless of infecting Plasmodium species and pregnancy status, who fulfil criteria for severe malaria, are unable to take oral therapy, have vital organ dysfunction, or high parasitaemia should received IV artesunate immediately, for a minimum of 24 hours. If IV artesunate is unavailable, IM artemether is an alternative, though it is considered less effective. IV quinine is reserved for situations where artemisinin-based therapies are not available, but it is typically not used as monotherapy. Parenteral antimalarial therapy for severe malaria should be followed by a full course of oral treatment.

Pregnant women in the first trimester who have severe malaria should receive IV quinine instead of artesunate.

Supportive Therapy: In addition to antimalarial drugs, supportive care (especially for severe cases) such as fluid therapy (preferable crystalloids at a conservative rate), Blood transfusion to those with severe anaemia, electrolyte correction, and management of complications (like hypoglycaemia, anaemia, and organ failure) are essential to the patient's recovery. Regular analgesics i.e paracetamol may be used.

Uncomplicated Malaria: Treatment depends on the infecting Plasmodium species and likelihood of drug resistance. Uncomplicated Falciparum, P. knowlesi and chloroquine-resistant P.vivax malaria should be treated with approved ACT (currently 6 by WHO) ACT i.e artemether-lumefantrine is the most commonly used even in the first trimester of Pregnancy. Other approved ACT include Artesunate-mefloquine, dihydroartemisinin-piperaquine, artesunate-sulfadoxine-pyrimethamine. It is recommended that administration with fatty food or milk is necessary to aid / optimise absorption. Uncomplicated chloroquine-sensitive P. vivax, P. malariae and P. ovale can be treated with chloroquine.

Anti-relapse therapy for P vivax or P. ovale malaria – Primaquine can be given after exclusion of G6PD deficiency. Please note that Primaquine is contraindicated in pregnant women, breastfeeding women and infants under 6 months..

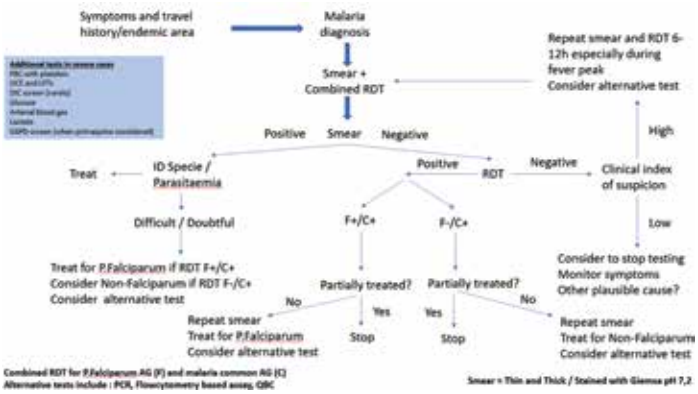
Vaccine: RTS,S/AS01E is the first malaria vaccine recommended by the World Health Organization (WHO) in 2021 for wide spread use in young children in areas of moderate and high P. falciparum. R21/ Matrix-M, a second malaria vaccine, has also been recommended by the WHO as safe and effective for use in children. The target group for these vaccines are children in regions with moderate to high transmission of malaria. **South Africa, however, does not fall within the category of regions recommended for these vaccines**, as malaria transmission in the country is low, therefore, the vaccine may not yet be implemented as a routine intervention in South Africa.

Conclusion

Plasmodium falciparum and *Plasmodium* vivax are the most significant species in terms of global malaria transmission and disease burden, but other species also contribute to the epidemiology of the disease in specific regions. Understanding the distribution and characteristics and the diagnostic modalities of these species is crucial for malaria control and elimination strategies, particularly as climate change and drug resistance continue to shape the global landscape of malaria transmission.

Appendix 1: Diagnostic criteria
Appendix 2: Algorithm for the management of malaria in South Africa
Appendix 3: Malaria tests requests:

Appendix 1: Diagnostic Criteria

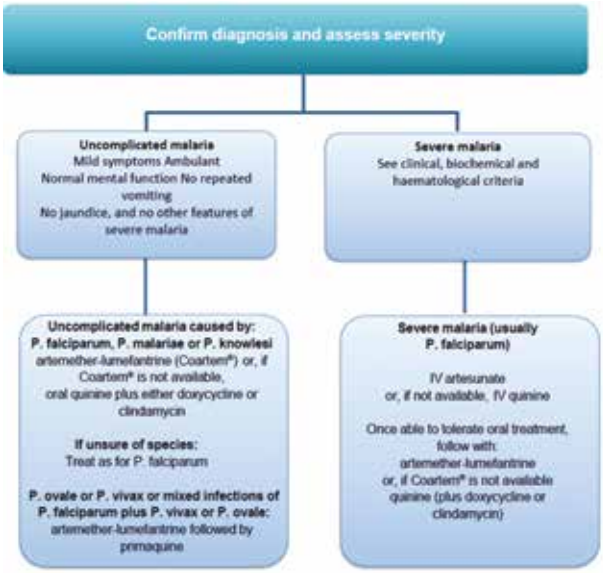


Other laboratory investigations that may be needed to support management of critically ill patients

FBC with platelets and differential count
Urea / Creatinine and electrolytes
Liver function tests
Arterial blood gas
DIC screen (PTT, INR, Fibrinogen)
CRP
Lactate

G6PD screen (when patient diagnosed with P.Ovale / Vivax and Primaquine treatment is being considered.

Appendix 2: Algorithm for the management of malaria in South Africa



Appendix 3: Malaria test requests

PathCare Gauteng region:

Malaria / Malaria screen / Malaria test: (1st presentation) – RDT and Morphology (thin and thick smears) +- QBC and/or Malaria PCR

Malaria follow-up patients – Morphology only

PathCare All other Provinces:

Malaria test as requested by the clinicians