GAUTENG DEPARTMENT OF HEALTH AND WELNESS
JOHANNESBURG HEALTH DISTRICT

MALARIA PREVENTION, DIAGNOSIS AND TREATMENT

20 NOVEMBER 2024

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Overview of the presentation

- Malaria-endemic destinations
- Preventative strategies
  - Bite avoidance
  - Chemoprophylaxis
- Diagnosis
- Treatment
- Pre-transfer management of severe malaria
- Notification
- Odyssean malaria
- Malaria vaccination
- Special considerations
  - Pregnancy and breastfeeding
  - Children
  - Immunocompromised individuals
  - Long-term prophylaxis

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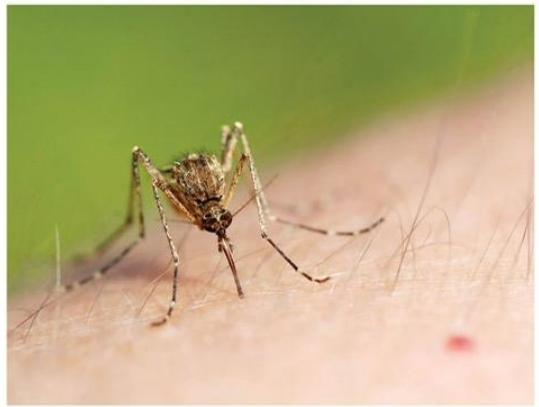
NEWS BULLETIN

OFFICIAL NEWSLETTER OF THE GAUTENG DEPARTMENT OF HEALTH 05 NOVEMBER 2023



Gauteng Health intensifies malaria awareness campaign

As the Southern African Development Community (SADC) observe Malaria Day on 6 November 2023 to raise awareness on the curable and preventable disease, the Gauteng Department of Health (GDoH) continues to target public transport nodes such as taxi ranks and bus stations to heighten education among people on prevention measures.

This comes as Gauteng hospitals reported 1 105 Malaria cases and 10 deaths from January to September 2023, as a result of the life-threatening disease spread to humans by mosquitoes in endemic areas.

The majority of people who were admitted and those who have demised as a result of the disease had travelled to Mozambique, Ethiopia, Nigeria, Zimbabwe, Zambia and Angola. These countries are known to be Malaria endemic regions within SADC.

In South Africa, Malaria endemic provinces include the Limpopo, Mpumalanga and Kwa-Zulu Natal provinces. However, non-endemic provinces like Gauteng still need to intensify awareness on how to prevent and manage the disease as many people who live in the province often visit these endemic regions, thus increasing the risk Malaria spreading.

Malaria symptoms include fever, headache, general body aches and pains, general body weakness, nausea, vomiting, loss of appetite, diarrhoea and the flu. It is important that people who notice any of these symptoms after visiting a malaria prevalent area visit their nearest clinic or doctor to get tested and treated for Malaria, as delay in treatment can lead to death.

While raising awareness about Malaria, the GDoH also offers those leaving South Africa to endemic areas Malaria chemoprophylaxis as part of efforts to prevent the infection rate. The Department also encourages travellers to report any symptoms of Malaria within 21 days of coming back from their trips for Malaria rapid test and early treatment.

When travelling to a Malaria endemic area, it is important for people to practice protective measures which include regular use of mosquito repellents, wearing of long trousers and long sleeve shirts, being indoors between dusk and dawn, sleeping in air-conditioned rooms or in a room with a fan and sleeping in insecticide treated nettings.

To ensure that awareness is ongoing at community level across the province, the GDoH continuously train Health Promoters at the districts and facilities on Malaria.

In addition to this, the GDoH has collaborated with the Doctors Without Borders to raise awareness and translate the information, education and communication on Malaria into Portuguese. This is due to 90% of the cases reported in Gauteng being of travellers from Mozambique.

> *"Gauteng hospitals reported 1105 malaria cases and 10 deaths from January to September 2023, as a result of the life-threatening disease spread to humans by mosquitoes in endemic areas."*

The MEC for Health and Wellness, Nomantu Nkomo-Ralehoko attended the 2023 Gauteng Youth AIDS Conference on 03 November 2023 at the Lakes Hotel and Conference Centre in Benoni.

The objective of the conference was to showcase and review existing HIV prevention, treatment and care programmes in the province and to give young people an opportunity to be involved in developing strategies for the HIV, TB and STI response.

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Introduction

- **>90 countries** reported **≈ 247 million infections** and **≈ 619 000 deaths** in 2021 (WHO, 2022).
- Travelers going to malaria-endemic countries are at risk of contracting the disease.
- The **risk** of acquiring malaria differs substantially from traveler to traveler and from region to region, even within a single country.
- This **variability** is a function of the intensity of transmission within the various regions and the itinerary, duration, season, and type of travel.
- **Risk** also varies by travelers' adherence to mosquito precautions and prophylaxis recommendations.
- Travelers to **rural areas** or staying in **accommodations without screens or air conditioning** are at greater risk.
- If malaria exposure is unavoidable, meticulous **non-drug measures and effective chemoprophylaxis** are both essential.
- NDOH recommends that travelers practice mosquito avoidance year-round in malaria risk areas and take malaria chemoprophylaxis during **September – May**.
- CDC, however, recommends chemoprophylaxis **at all times of the year**.
- Rare cases of so-called Odyssean, "taxi," or "suitcase" malaria have been reported in Gauteng Province, likely related to relocation of infected mosquitoes from endemic areas.
- Plasmodium species are transmitted by the bite of an infective female Anopheles mosquito.
- Occasionally, transmission occurs by blood transfusion, needle sharing, nosocomial, organ transplantation, or vertically from mother to fetus.
- Travelers can become infected even if they had malaria before, and they still need to take preventive measures - **Tolerance** acquired through continuous exposure to malaria is quickly lost.

Malaria-endemic destinations in Africa and the Middle East

(CDC, 2023)

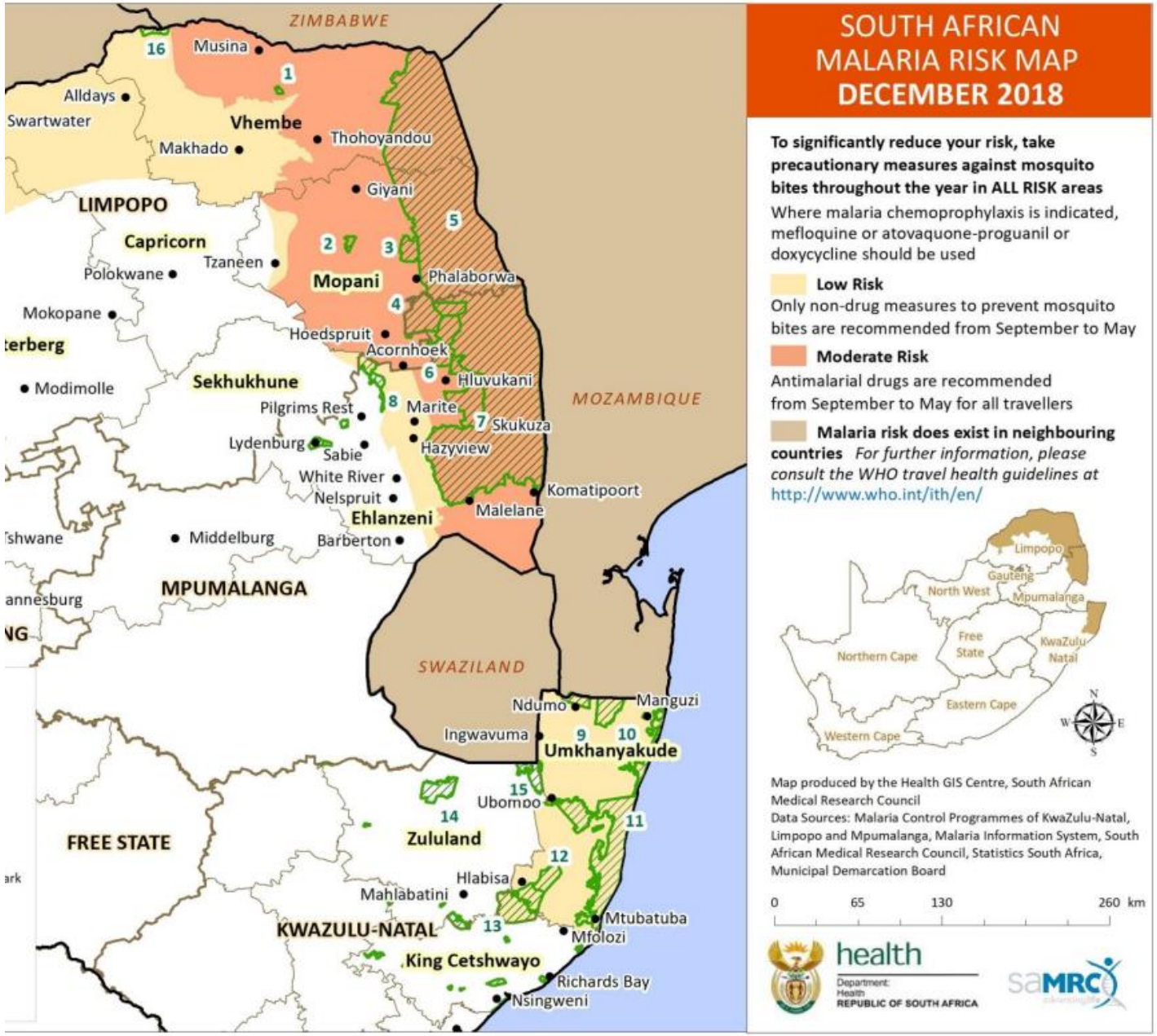
Malaria-endemic destinations in:

Asia & Oceania /
The Americas & Caribbean

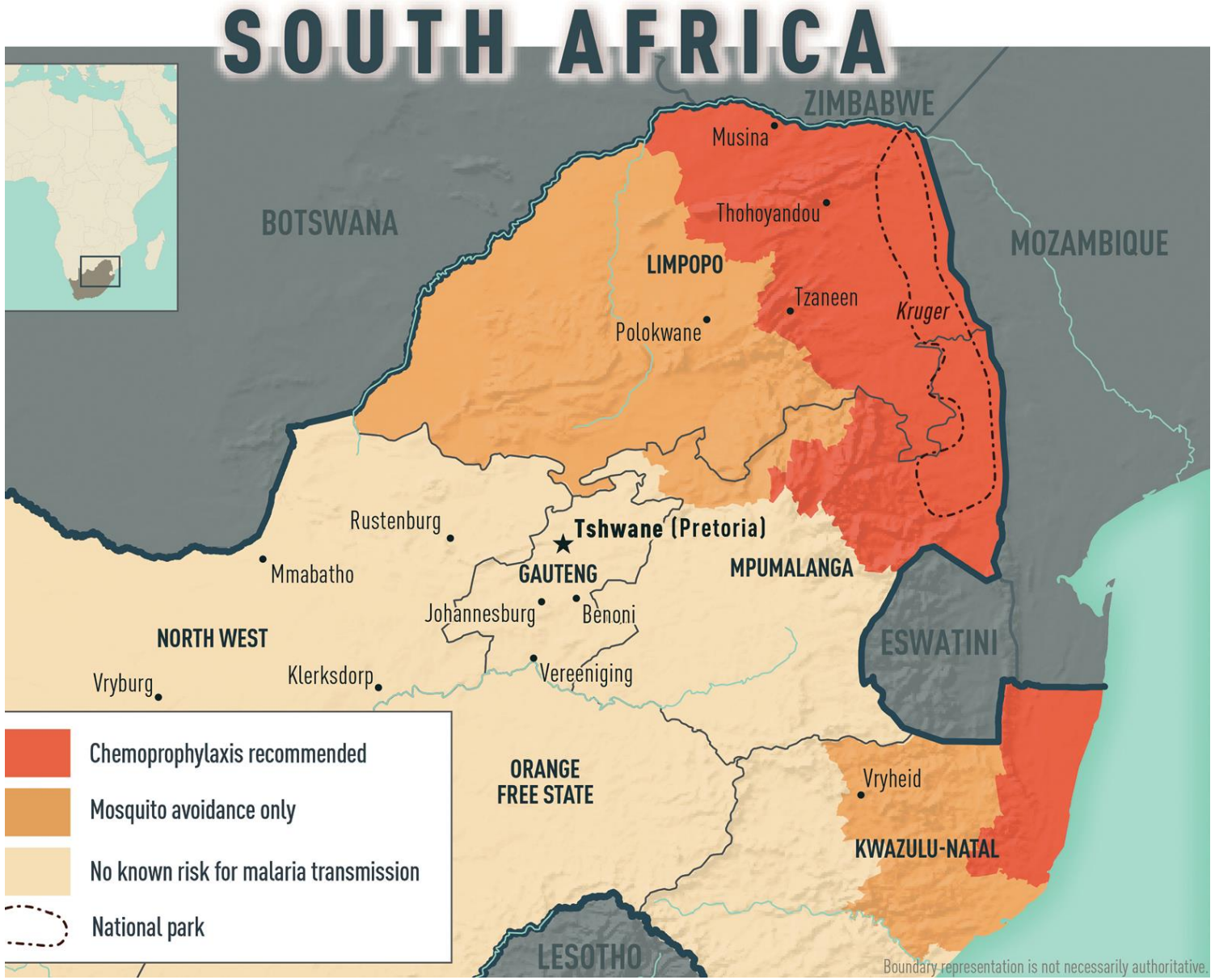
(CDC, 2023)

Malaria risk in the three endemic provinces of South Africa

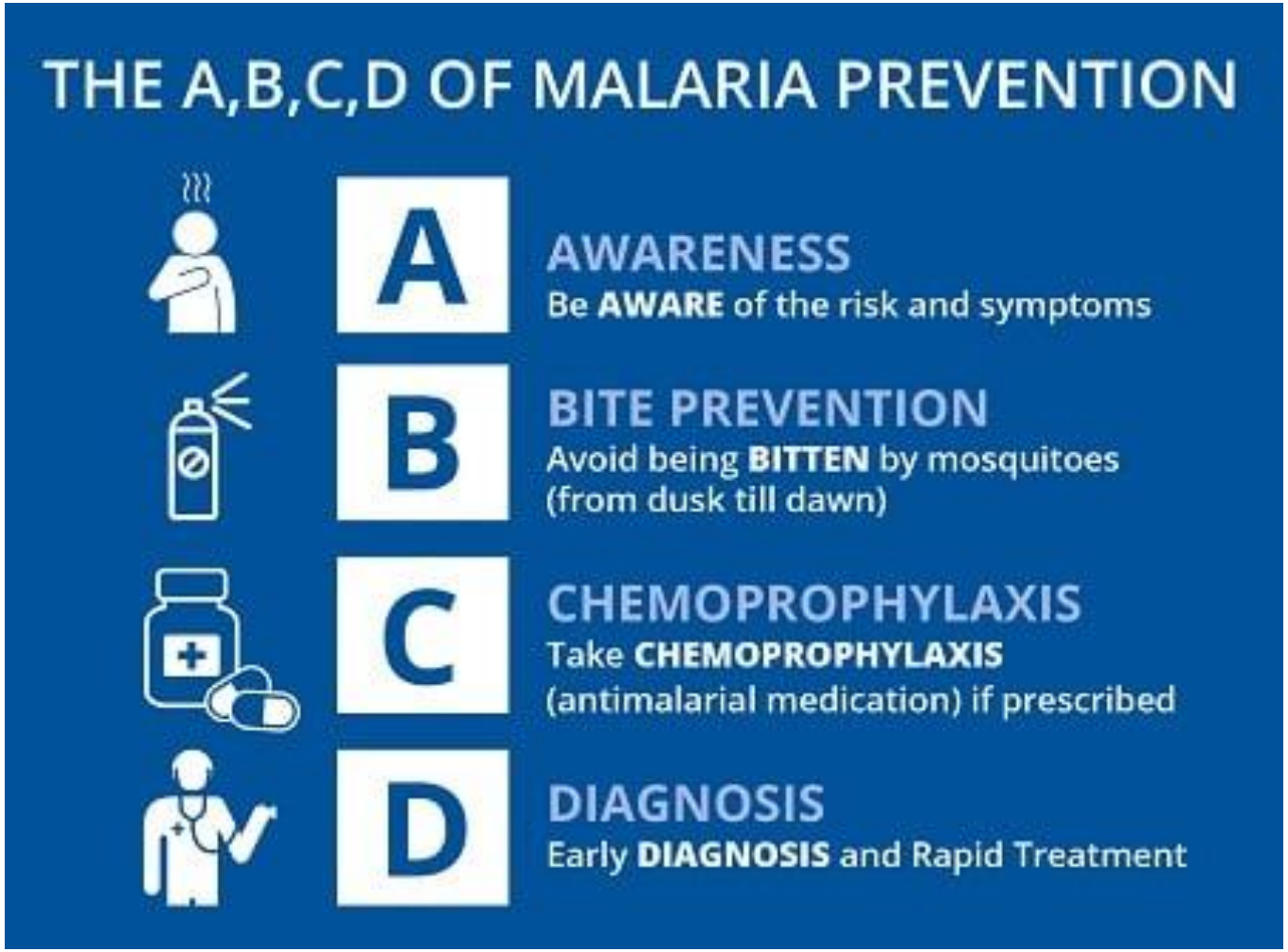
(NICD, 2018)



Malaria prevention in South Africa



(CDC, 2023)



ABCD of Malaria prevention

Persons at particular high risk of severe Malaria

- Pregnant women
- Infants and young children
- Older persons > 60 years
- Immunocompromised patients, e.g., those on long-term steroid therapy or chemotherapy, AIDS patients, and patients who had a splenectomy.

Mosquito bite avoidance / Non-drug measures

- Because of the nocturnal feeding habits of Anopheles mosquitoes, malaria transmission occurs primarily **between dusk and dawn**.
- Travelers can reduce contact with mosquitoes by remaining in enclosed air-conditioned rooms or well-screened areas, sleeping under mosquito nets (preferably insecticide-treated), using an effective insecticide spray or mosquito coils in living and sleeping areas during evening and nighttime hours, and wearing clothes that cover most of the body.
- All travelers should use an **effective mosquito repellent**.
- Repellents should be applied to **exposed parts** of the skin.
- If travelers are also wearing sunscreen, they should **apply sunscreen first and insect repellent second**.
- In addition to using a topical insect repellent, a permethrin-containing product can be applied to **mosquito nets and clothing** for additional protection against mosquitoes.
- Mosquito repellant–impregnated clothing also is available.
- **Mosquitos also transmit Zika virus, West Nile virus, Chikungunya virus, and Dengue**

How to stay protected and prepared

- When outdoor for extended periods, buy clothing saturated with insecticide or spray / soak your outer layer clothing with permethrin
- Pack **insect repellent** containing 20% - 30% DEET
- Pack antihistamines to relieve swelling and itching resulting from insect bites
- Apply insect repellant to all **exposed areas** of your skin, avoiding your face and hands
- **Reapply** insect repellant according to the manufacturer’s directions
- Seek medical attention when you develop flu-like symptoms, fever, a rash or signs of an allergic reaction

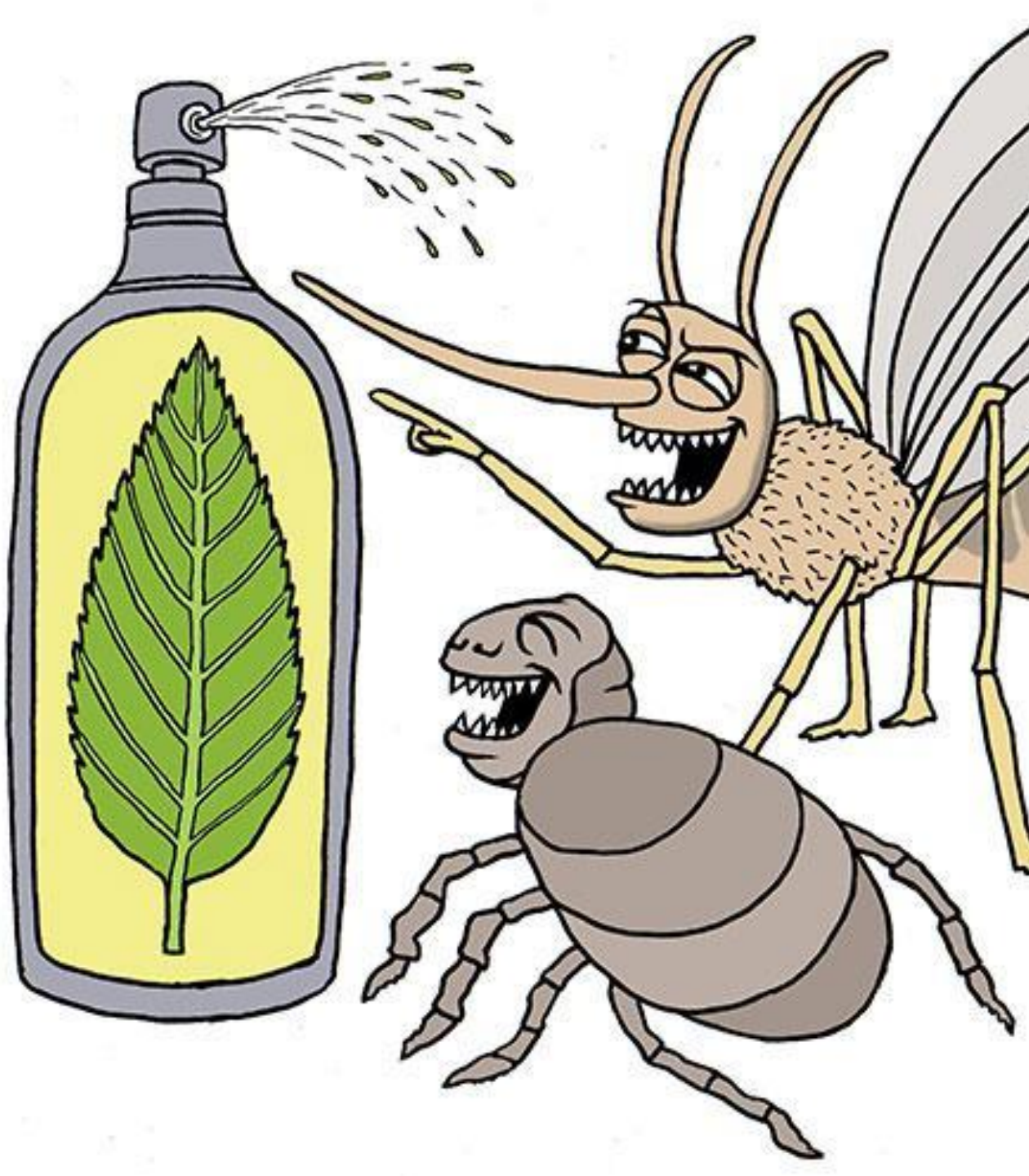
Preventing mosquito bites

- Wear **long-sleeved shirts and long trousers in light colors** (white or beige) – dark clothing attracts mosquitos
- **Avoid wearing perfume** or after-shave lotion – scents attract mosquitos
- Close all windows and door screens
- Use **mesh** that is small enough to prevent mosquitos from entering
- To reduce indoor bites, stay in accommodation with **air conditioning** – mosquitos are deterred by breezes and colder temperatures
- Use pyrethrin (a natural plant-based insecticide) in living and sleeping areas, including bed nets
- Cover food and utensils while spraying and allow vapor to settle before returning
- **Bed nets also protect against ticks, beetles, flies, spiders and other insects**
- **Insecticide-treated beds** are more effective than untreated nets

Myths

Garlic, clove oil, citronella bracelets and candles, ultraviolet lights or herbal treatment have not been proved to prevent mosquito bites or malaria infection.

Patients do not develop natural immunity against infection.



Chemoprophylaxis

Choice of chemoprophylaxis should be individualized, considering:

- **Resistance** – Sub-Saharan Africa: Chloroquine-resistant *P. falciparum*, South-East Asia: multidrug resistance with reduced effectiveness of mefloquine prophylaxis
- **Transmission intensity** is reduced during dry seasons, at high altitude and in developed city centers
- **Length of stay** increases risk
- **Age** affects drug selection and dose
- **Comorbidities**, immune status, concurrent medication, and previous experience with use of chemoprophylaxis may influence drug selection
- **No antimalarial agent is 100% effective** - travelers should seek immediate medical attention for “flu-like” symptoms
- Typical time from infection of falciparum malaria to symptoms is 7 – 30 days but may be prolonged when taking chemoprophylaxis, and up to a year for *P. ovale* and *P. vivax*

Atovaquone / Proguanil

- Fixed-dose prophylaxis of choice
- Well-tolerated and effective
- Adherence is improved by shorter prophylactic course
- 250 / 100 mg po **taken with food daily**, starting 1 – 2 days before entering and until 7 days after leaving

Doxicycline

- Prophylactic agent of choice for non-pregnant travelers > 8 years who can tolerate the drug
- Adults & > 8 y dose: 100 mg po **daily**
- Pediatric dose: 2 mg / kg **daily**
- 24 – 48 h before entering the area and **continue until 4 w** after leaving the area
- Recommended by NDOH and available without prescription (**S2**), for periods not exceeding 4 months
- Causes **milk teeth staining, enamel hypoplasia and bone growth inhibition** in fetus

Mefloquine

- Blood schizonticide active against the asexual stages of *P. falciparum* and *P. vivax*
- **Neuropsychiatric, cardiovascular and optic side-effects**
- Only recommended prophylactic agent in pregnancy if travel to a malaria-risk area is unavoidable
- **No longer marketed in SA**
- May be obtained on a named-patient basis after **SAHPRA approval**
- **Once weekly** with food initiated 1 – 2 weeks before entering and up to 4 weeks after leaving:
  - 5 – 9 kg: 62.5 mg
  - 20 – 30 kg: 125 mg
  - 31 – 45 kg: 187.5 mg
  - > 45 kg: 250 mg

Chloroquine

- Rapidly acting against blood schizonts
- Widespread resistance precludes against its use against *P. falciparum*
- May be considered for prophylaxis in areas **where only *P. vivax / ovale* occur**
- 300 mg po taken with food **weekly**, initiating 1 week before entering and continued until 4 weeks after leaving

Not recommended as chemoprophylaxis:

- Sulfadoxine / pyrimethamine
- Quinine
- Halofantrine
- Artemisinin derivatives
- Dapsone / pyrimethamine
- Chloroquine / proguanil

Stand-by emergency treatment (SBET)

- Those travelling for **> 1 week to areas without medical services** should consider carrying a full 6-day course of artemether / lumefantrine as SBET
- Associated with risks - patients should be given detailed **written instructions**

Pregnancy and lactation

- Pregnant women should be discouraged from entering malaria areas
- If exposure is unavoidable, non-drug measures and chemoprophylaxis should be advised
- **Mefloquine** recommended by CDC as preferred chemoprophylaxis against *P falciparum* for pregnant and breastfeeding women (Section 21)
- Mefloquine is excreted in breastmilk but the risk to the infant is minimal
- Breastfed infants are not adequately protected by the mother's prophylaxis and require their own prophylaxis
- **Doxycycline and Atovaquone / Proguanil are both contraindicated in pregnancy**
- Chloroquine has unacceptably low efficacy against *P. falciparum* and therefore cannot be recommended

Pediatrics

- **Children < 5 y should avoid going to high-risk malaria areas**
- If exposure is unavoidable, non-drug measures and chemoprophylaxis should be advised
- Pediatric formulation of **atovaquone / proguanil** is registered for children weighing > 11 kg, however **removed from the market**, and adult tablets cannot be split
- Mefloquine is contraindicated in children weighing < 5 kg, but Section 21
- Doxycycline should be avoided in children < 8 years of age

Long-term prophylaxis

Strategies for long-term prophylaxis include:

- Sequential regimens with different medications,
- Prophylaxis targeting high transmission intensity periods, or
- Prompt diagnosis and treatment locally or SBET

<u>If tolerated:</u>

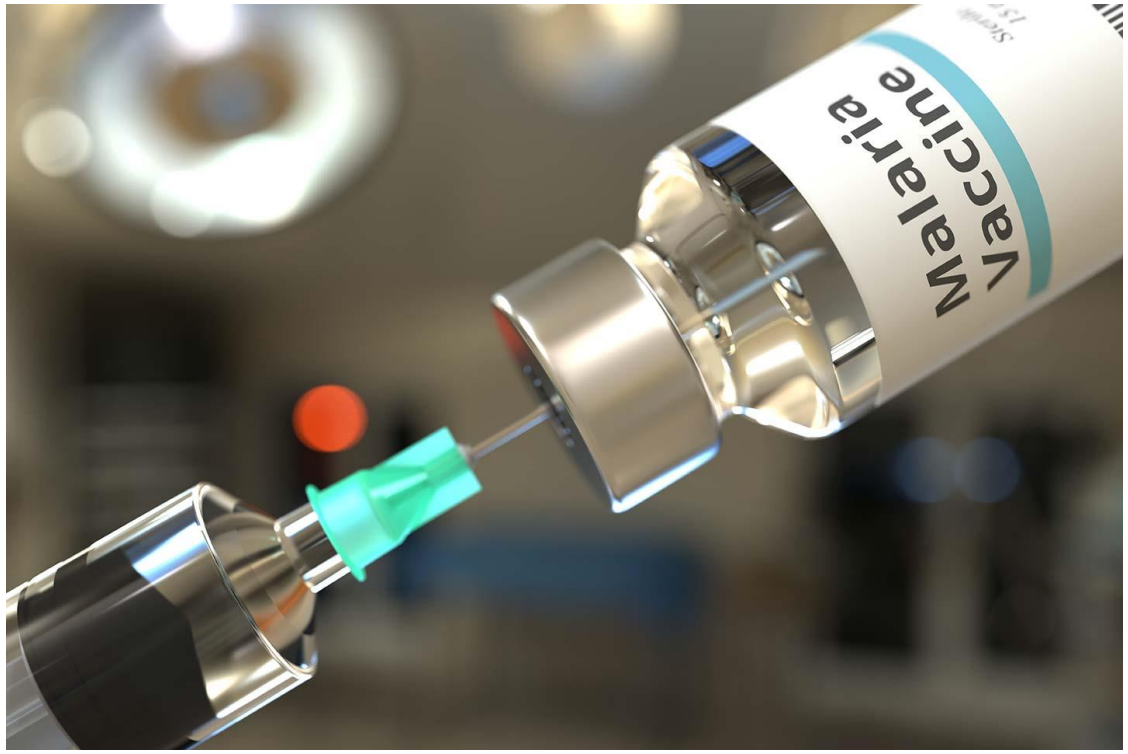
- Mefloquine can be used for up to 3 years
- Doxycycline for up to 2 years
- Atovaquone / proguanil for up to 1 year

Addressing concerns about side-effects from prophylaxis

- Prophylaxis can be **started earlier** if the traveler has concerns about tolerating a particular medication. For example, mefloquine can be started **3–4 weeks in advance** to allow potential adverse events to occur before travel. If unacceptable side effects develop, the clinician has time to **change the medication** before the traveler's departure.
- The drugs used for antimalarial prophylaxis are generally well tolerated.
- Minor side effects usually do not require stopping the drug.
- Clinicians should determine if symptoms are related to the medicine and make a medication change if needed.

Malaria vaccine

- Since 2019, Ghana, Kenya and Malawi have been delivering the malaria vaccine through the Malaria Vaccine Implementation Programme (MVIP)
- RTS,S/AS01 (brand name Mosquirix) is the first malaria vaccine approved for public use.
- Requires at least **three doses in infants by age 2**, with a **fourth dose** extending the protection for another 1–2 year
- Reduces risk of developing malaria in vaccinated population by up to 44%
- **Only relevant to high-transmission country settings**



(WHO, 2021)

Preventative measures summary

- Use the **A, B, C, D** approach – Recommend patient visits a **travel clinic** before departure
- Preventing malaria involves striking a **balance between effectiveness and safety**: ensuring that all people at risk for infection use the recommended prevention measures and preventing rare occurrences of adverse effects.
- Conduct an individual **risk assessment** for every traveler by collecting a **detailed travel itinerary**, including countries, specific areas to be visited in those countries (e.g., cities, rural areas, both), types of accommodation, season, and style of travel.
- Modify the risk assessment depending on **traveler characteristics** (e.g., pregnancy, underlying health conditions) and malaria **characteristics at the destination** (e.g., intensity of transmission, local parasite resistance to drugs).
- Depending on the level of risk, it **might be appropriate to recommend no specific interventions, mosquito avoidance measures only, or mosquito avoidance measures plus chemoprophylaxis.**

Epidemiology

- *Plasmodium falciparum* (*P. falciparum*) accounts for >90% Malaria cases in Southern Africa and may be associated with **severe and fatal disease**.
- The remainders are due to P. ovale, P. vivax, or P. malariae. Occasionally mixed infections occur.
- Almost all South Africans, including residents of seasonal malaria transmission areas in the country, are **non-immune** and are therefore at increased **risk of developing severe malaria**.
- Malaria transmission mainly occurs up to the 2 000 m above sea level but can also occasionally affect areas up to 2 300 m **elevation**.
- Pregnant (and post-partum) women, young children, the elderly, splenectomised and immunocompromised persons (including HIV-infected persons) are the groups at highest risk for the development of severe P. falciparum malaria.
- **Sickle cell trait** (AS) confers partial protection against lethal Plasmodium falciparum malaria.
- Children with SCA are innately protected against classic severe malaria. However, even low-level infections can precipitate severe anaemic crises that would likely prove fatal without rapid access to blood transfusion services (Uyoga, 2022).

Malaria treatment objectives

The main objectives of malaria treatment are to:

- Prevent mortality
- Prevent disease progression and development of severe malaria
- Reduce morbidity
- Eliminate parasitaemia and stop further transmission
- Limit the emergence and spread of drug resistance

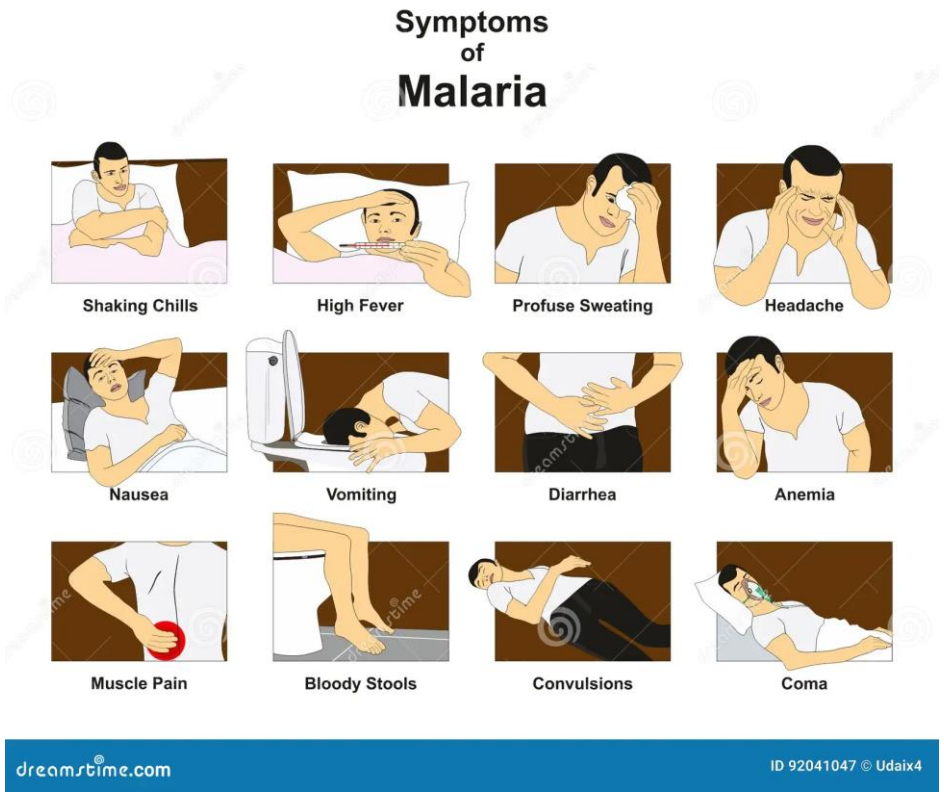
Management principles

- The diagnosis and management of malaria is urgent.
- As signs and symptoms of malaria are very non-specific, a **high index of suspicion** is the most important element in the diagnosis of malaria.
- Malaria should be suspected in any person presenting with any of the suggestive symptoms, who has a history of travel to, or residence in a malaria transmission area.
- **Delayed diagnosis, underassessment of disease severity and inappropriate treatment** are associated with significantly increased morbidity and mortality.
- Classically, malaria presents with fever, rigors, headache and body pains, but the clinical features are non-specific and may be confused with many other diseases, especially influenza.
- A **definitive diagnosis** should be made promptly by demonstrating the parasite on microscopy of a blood smear or by using a malaria rapid diagnostic test.
- **Disease severity** should be assessed carefully with both clinical and laboratory tests.
- Malaria is a **notifiable disease**.

Symptoms and signs

Common malaria symptoms and signs include:

- Fever, chills, perspiration, rigors (cold shivers/hot sweats)
- Headache
- Muscle/joint aches
- Malaise
- Lethargy, lassitude, fatigue
- Loss of appetite (in older children and adults),
  Poor feeding (in young children)
- Abdominal discomfort, diarrhoea, nausea, vomiting
- Cough (in young children)
- Splenomegaly (in patients from areas of high intensity malaria transmission)



Onset

- Symptoms and signs of falciparum malaria may present as **early as seven days after exposure**, with a usual **range of 10 to 21 days** elapsing after being bitten by an infected vector mosquito.
- **Longer incubation periods** may occur in patients who have failed chemoprophylaxis (usually due to poor adherence or inappropriate chemoprophylaxis) or have been on selected antibiotics (e.g. cotrimoxazole, tetracycline, macrolides, chloramphenicol and quinolones). Very rarely, incubation periods for P. falciparum of six to 18 months have been recorded.
- Malaria due to infections with P. vivax, P. ovale or P. malariae can take **up to 12 months** to first manifest clinically, with relapses occurring months or even years later, if primaquine is not taken to ensure radical cure.

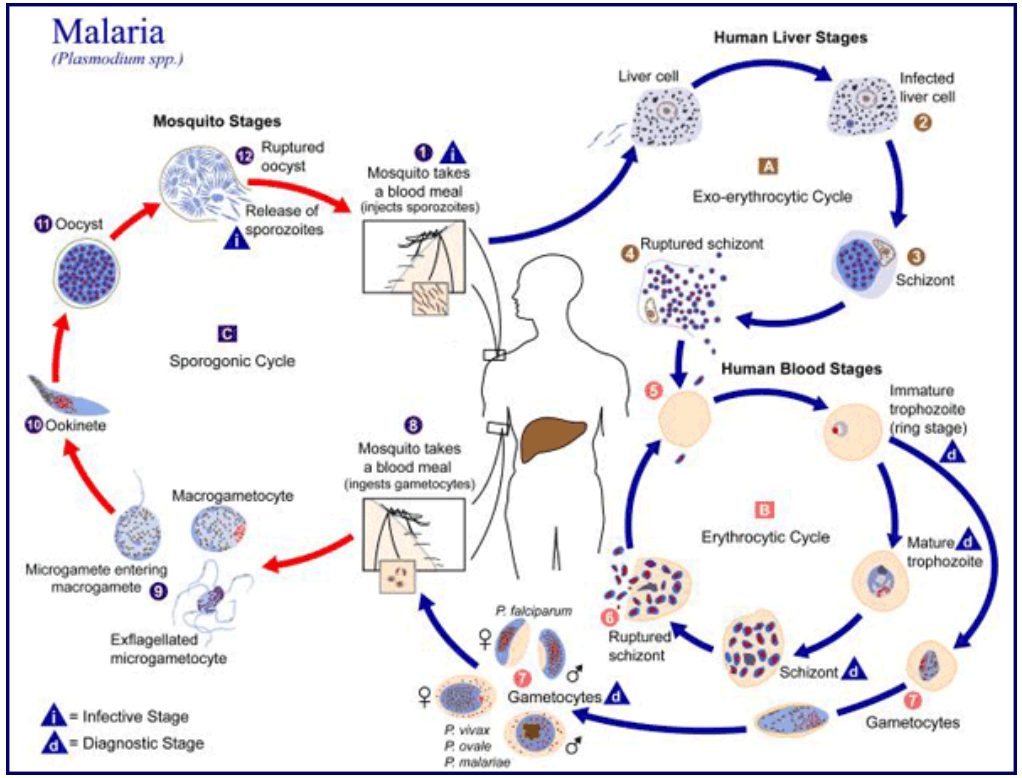
Differential diagnosis

Presentation of falciparum malaria is very variable and may mimic many other diseases (and vice versa) including:

- Influenza
- Viral hepatitis
- Meningitis
- Encephalitis
- Septicaemia
- Typhoid fever
- Tick bite fever
- Gastroenteritis
- Viral haemorrhagic fever
- Trypanosomiasis
- HIV seroconversion illness
- Urinary tract infection
- Relapsing (Borrelia species spirochetes)

Disease progression

- Non-immune patients with uncomplicated malaria are at significant risk of **disease progression to severe falciparum malaria**.
- Life-threatening complications can develop rapidly in these patients.
- These complications occur almost invariably because of **delay in diagnosis and/or delay in treatment of an uncomplicated infection, the use of ineffective therapy or under-dosing with effective drugs**.



Malaria-related Neurocognitive Deficits and Behavior Alterations

Survivors of severe malaria

Neurological sequelae

- Motor deficits[5,8,14,16,17]
- Ataxia[8,14,17]
- Paresis[8]
- Movement disorders[8,17]
- Seizure[1,4,5,8]
- Visual impairments[8,14,17]
- Hearing impairments[14]
- Speech or language impairments[3,4,5,8,14,16,17]
- Development delay[16]

Cognitive deficits

- Attention deficits[4,5,6,7,11,13]
- Learning difficulties[12,19]
- Cognitive ability deficits[11,13,16,17,18,19] (fine motor, visual reception, receptive and expressive language)
- Memory deficits[1,2,4,5,6,10]
- Non-verbal function deficits[3,4,5,13]

Behavioral alterations

- Emotional reactions[15]
- Disruptive behaviors[15,18]
- Attention deficit and hyperactivity disorders[14]
- Conduct disorders[14]
- Oppositional defiant disorders[14]
- Sleep problems[15]
- Anxiety[14,15]

Diagnosis

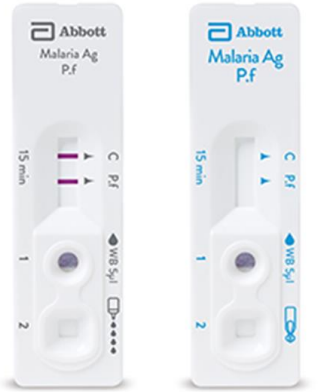
- A **diagnosis of malaria cannot be confirmed or excluded clinically.**
- Since the clinical presentation is **non-specific and may mimic many other diseases**, each patient's blood should be examined immediately using a **malaria antigen rapid diagnostic test** (RDT) or **microscopy of thick and thin 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-hour intervals**. Repeat tests should continue until the diagnosis is confirmed, the patient has recovered, or another definitive diagnosis has been made.
- A blood test for parasites should be done **irrespective of the time of the year or whether or not the patient has taken chemoprophylaxis or travelled** to a malaria endemic area.

Laboratory investigations

- In the majority of malaria cases, examination of correctly stained blood smears will reveal malaria parasites.
- Examination of the peripheral blood smear will give an indication of the parasite density as well as the species of parasite. **High levels of parasitemia (>4% or equal to or more than three + or more than 100 000 asexual parasitized red blood cells/µl) should be treated as severe malaria.**
- Importantly, the converse may not be true, with **severe disease sometimes occurring with low parasitaemias in the peripheral blood**.
- The interpretation of a low parasite count must always be considered in conjunction with the patient's clinical condition and other laboratory results

Rapid Diagnostic Tests

- A number of commercial rapid diagnostic tests (RDTs) are available for early diagnosis in health facilities where microscopy is not immediately available.
- These RDT kits detect parasite antigens, namely, **histidine-rich protein** 2 (or parasite lactate dehydrogenase or aldolase).
- **Most RDTs will only detect *P. falciparum***, although some can detect the other malaria species but are less sensitive for these.
- The *P. falciparum*-specific RDTs are generally highly sensitive; however, performance is dependent on the correct storage, usage, interpretation of results and quality of RDT used.
- The test **may be negative early in the disease**, and false positives may be encountered occasionally.
- RDTs should be **used only for diagnosis** of acute malaria infections, and not for follow-up, as they may **remain positive for several weeks, even after successful treatment**.



Diagnostic approach

- If the diagnosis of malaria cannot be confirmed (unavailability of RDTs and microscopy or negative test results), the decision to commence malaria therapy should be made on clinical grounds, based on whether exposure to malaria parasites was possible and the severity of the clinical features.
- In cases of severe malaria, a blood smear or rapid malaria test is likely to be positive.
- However, occasionally patients with severe malaria **may have a negative smear** due to **sequestration of parasitized red blood cells.**
- In patients who are treated empirically for malaria, it is imperative to collect a blood specimen before treatment and to continue to look for alternative diagnoses and to follow up patients very carefully.
- **A malaria smear is indicated in patients with malaria symptoms and a negative RDT, to exclude non-falciparum malaria**.

Confirm diagnosis and assess severity

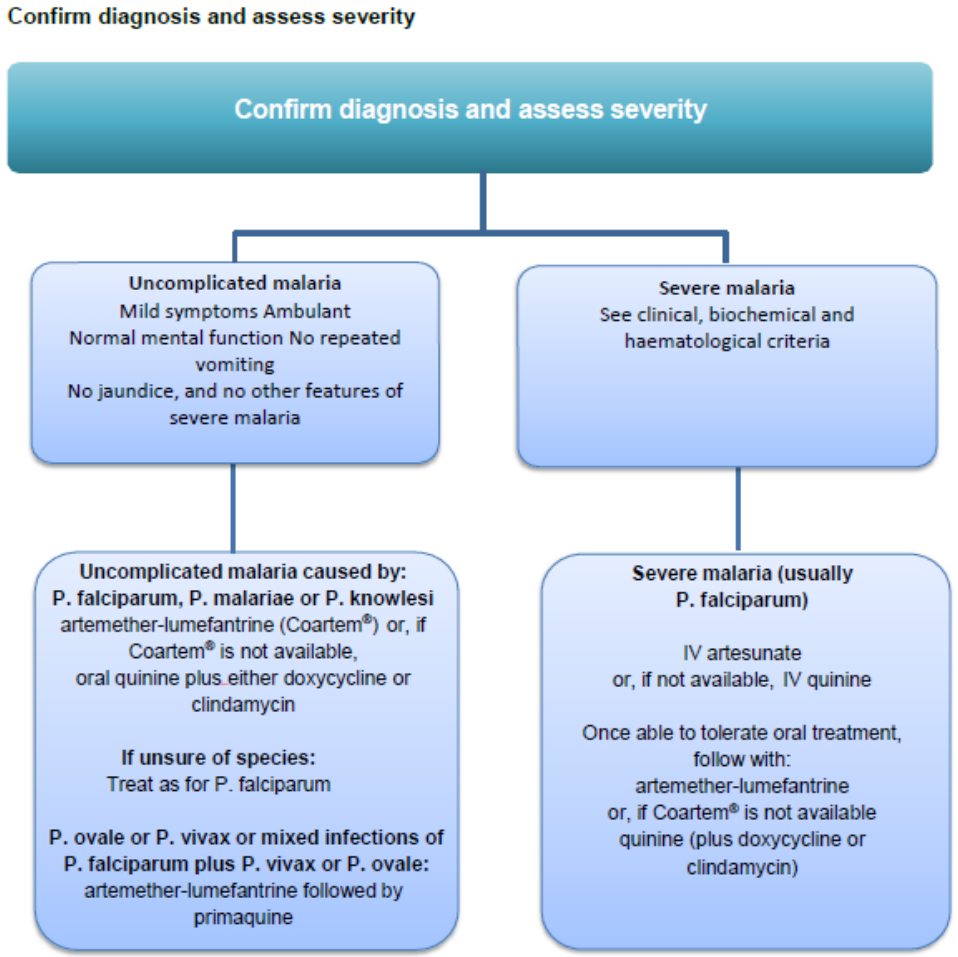


Figure 1. Algorithm for the management of malaria in South Africa

Uncomplicated malaria

- For uncomplicated malaria, artemether-lumefantrine (**Coartem®)** is recommended for first-line therapy.
- **Oral quinine plus either doxycycline or clindamycin** should only be used if **artemether-lumefantrine is unavailable or contraindicated**.
- High-level resistance precludes the use of both chloroquine and sulfadoxine-pyrimethamine for the treatment of falciparum malaria.
- Given its associated safety concerns, halofantrine should not be used.

Key patient information for outpatient treatment

- Take all doses as directed, even if feeling better sooner.
- Artemether-lumefantrine should be taken with a **fat-containing meal or drink**
- It is important that the patient drinks enough fluids, and takes paracetamol (not anti-inflammatories as it increases the risk of renal failure) to treat their fever
- The patient should expect **improvement of symptoms within 24 to 48 hours** and to return to the health facility if they remain unwell or their temperature is not settling by day three
- The patient should return to the health facility immediately if vomiting, or if the patient deteriorates in any way (e.g., becomes sleepy, confused, jaundiced)

Dosage of Artemether-Lumefantrine

Table 1. Dosage of artemether-lumefantrine

ARTEMETHER-LUMEFANTRINE (oral) One tablet contains artemether 20 mg plus lumefantrine 120 mg.	**5 -<15 kg#:** One tablet stat, followed by one tablet after eight hours and then one twice daily on each of the following two days (total course = six tablets) **15-<25 kg:** Two tablets stat, followed by two tablets after eight hours and then two twice daily on each of the following two days (total course = 12 tablets) **25-<35 kg:** Three tablets stat, followed by three tablets after eight hours and then three twice daily on each of the following two days (total course = 18 tablets) **35-<65 kg:** Four tablets stat, followed by four tablets after eight hours and then four twice daily on each of the following two days (total course = 24 tablets). **>65 kg*:** Dose as for those above 35 kg, although inadequate experience in this weight group justifies closer monitoring of treatment response. *NOTE: Administer with food/milk containing at least 1.2 g fat (e.g. ~100ml milk) to ensure adequate absorption.*

*WHO states that it can be used for children weighing less than 5 kg. (See 8.2.1) A flavoured dispersible tablet has been formulated for use in young children, but is not yet registered for use in South Africa.*

** An adult tablet containing 80mg artemether and 480 mg lumefantrine has been formulated that allows adults to be dosed with one tablet stat, followed by one tablet after eight hours and then one tablet twice daily on each of the following two days (total course = six tablets). This formulation is not yet registered for use in South Africa.*

Special consideration for patients weighing > 85 kg

- Patients weighing more than 85 kg may be at an increased risk of treatment failure
- Advise extending the treatment course to **FIVE days of Artemether-Lumefantrine**
- Administering FOUR tablets per dose, given twice daily for a total of 10 doses / 5 days (off-label recommendation).

When artemether-lumefantrine is not available or is contraindicated

Table 2. Doses of quinine (plus either doxycycline or clindamycin)

QUININE (oral) One tablet usually contains 300 mg quinine sulphate	10 mg salt/kg body weight every eight hours for seven days. In the past, maximum doses have been recommended, but there is no evidence or justification for this practice. For obese patients, less of the drug is often distributed to fat than other tissues; therefore they should be dosed on an estimate of lean body weight or ideal body weight. Patients who are heavy but not obese require the same mg/kg doses as lighter patients. As data is limited on the relationship between dose, drug exposure and treatment outcome in large and obese patients, treatment providers should follow up their treatment response more closely whenever possible.
DOXYCYCLINE (oral) One capsule / tablet contains 50 or 100 mg doxycycline	Use in combination with quinine: 100 mg (or 2.2 mg/kg in children) twice daily for at least seven days. NOTE: Avoid in pregnancy and children under eight years old.
CLINDAMYCIN (oral) One tablet contains 150 mg clindamycin	Use in combination with quinine in pregnancy and children under eight years: 10 mg/kg twice daily for seven days

- Quinine therapy should be continued for seven to ten days.
- Quinine should ideally be used as directly observed treatment of inpatients, due to the poor tolerability and thus poor adherence with this seven-day regimen.

Quinine side-effects

- Minor adverse effects, causing a syndrome known as **cinchonism** (mild hearing impairment - notably high tone deafness), tinnitus, headache, nausea and slight visual disturbances) occur in up to 70% of patients with therapeutic quinine concentrations and are not an indication to discontinue therapy.
- **Hypoglycemia** is the most frequent serious adverse reaction, and it is particularly common in young children, pregnant women and elderly patients.
- **Quinine toxicity** presents with central nervous system (CNS) disturbances (primarily visual and auditory) and cardiovascular abnormalities (hypotension, heart block, ventricular arrhythmias) and can be confused with severe malaria.
- **Cardiotoxicity is particularly related to rapid infusion of quinine**, which should always be given by **slow infusion over two to four hours**.
- **Hypersensitivity reactions** to quinine have been reported, including urticarial rash, bronchospasm, flushing, fever, antibody-mediated thrombocytopenia, haemolytic anaemia and haemolytic-uraemic syndrome.
- Hepatic injury and psychosis occur very rarely.

Treatment failure

May be due to:

- Parasite resistance to the antimalarial drug used
- Under-dosing
- Vomiting of oral medication
- Non-compliance with medication
- Failure to take fatty food or milk with artemether-lumefantrine, leading to poor absorption of lumefantrine component
- Re-infection (apparent treatment failure)
- Relapse due to *P. ovale* or *P. vivax*, because of failure to take primaquine for radical cure of hypnozoites

Definite indications for hospital admission – Refer patient urgently

- **Any feature of severe malaria**
- **Danger signs**
- **High risk groups**
- **Suspected treatment failure (including reappearance of parasites within six weeks of treatment)**

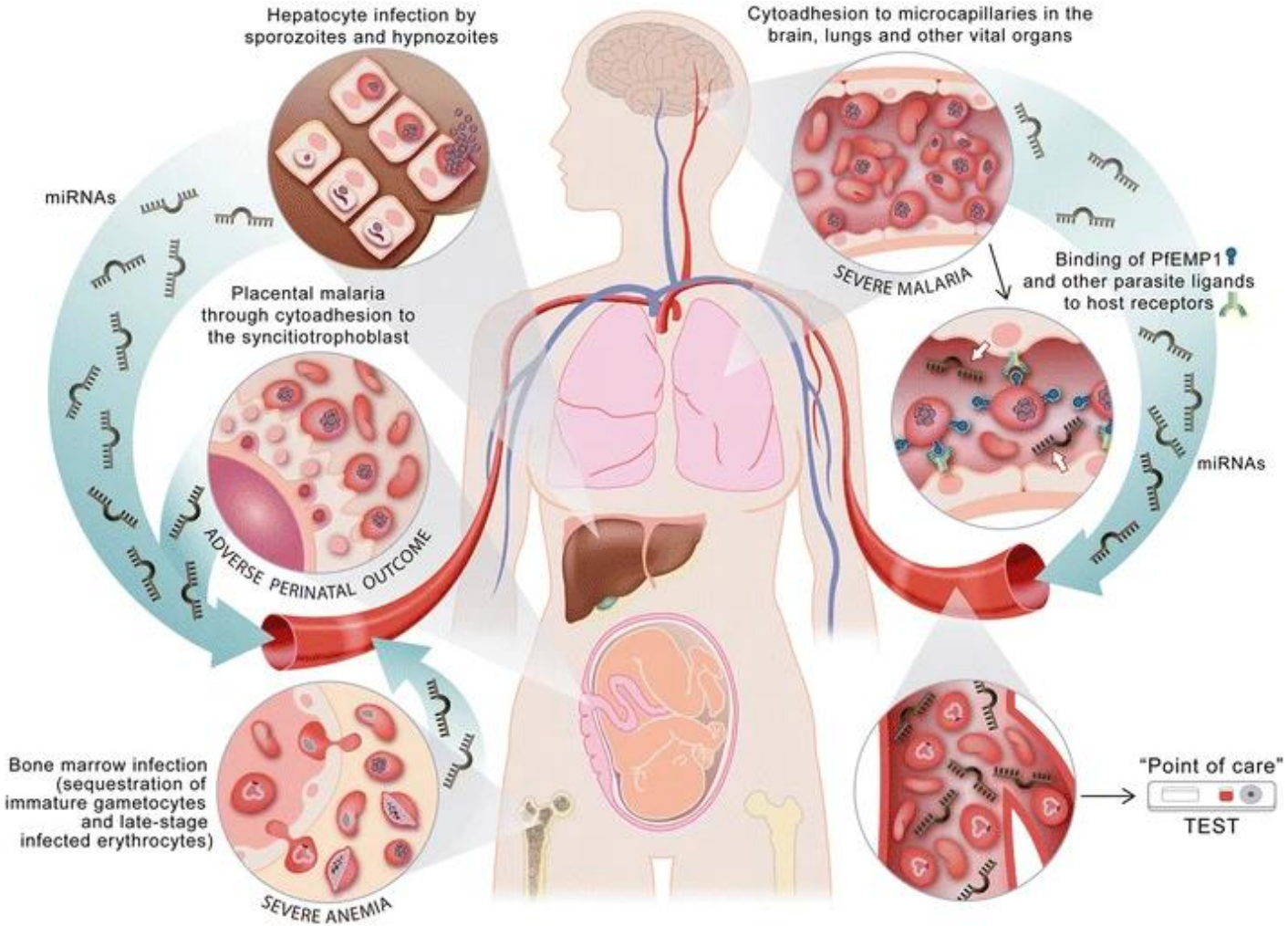
Danger signs include:

- inability to drink or breastfeed
- repeated vomiting
- recent history of convulsions
- lethargy
- unable to sit or stand

High risk groups

- Pregnant and postpartum women
- Infants and young children
- Elderly persons (older than 65 years)
- Splenectomised persons
- Immunocompromised persons (including HIV-infected)
- Persons with comorbid conditions

Cytoadherence – Sequestration specific to Plasmodium falciparum



Severe malaria

- **Severe malaria is a medical emergency**.
- Unless falciparum malaria is promptly diagnosed and treated, the clinical picture may deteriorate rapidly.
- **Severe malaria carries a 10 – 40% case fatality rate**, often despite treatment.
- Patients should be treated promptly with **intravenous (or intramuscular) artesunate or quinine** (if artesunate not available) in the **highest level of care available**.
- For severe malaria, intravenous artesunate (or if contraindicated or unavailable, intravenous quinine) **for at least 24 hours**, is recommended and should be followed by a full treatment course of artemether-lumefantrine as soon as the patient can tolerate oral treatment.
- Patients with **severe malaria all require hospital admission**.
- The major complications of malaria include **cerebral malaria, hypoglycemia, anemia, renal failure, acute respiratory distress syndrome (ARDS) and metabolic acidosis**. These complications carry high mortality rates especially in children, pregnant woman and in those living with HIV and AIDS. These complications require specific management and close monitoring.

Clinical features of severe malaria

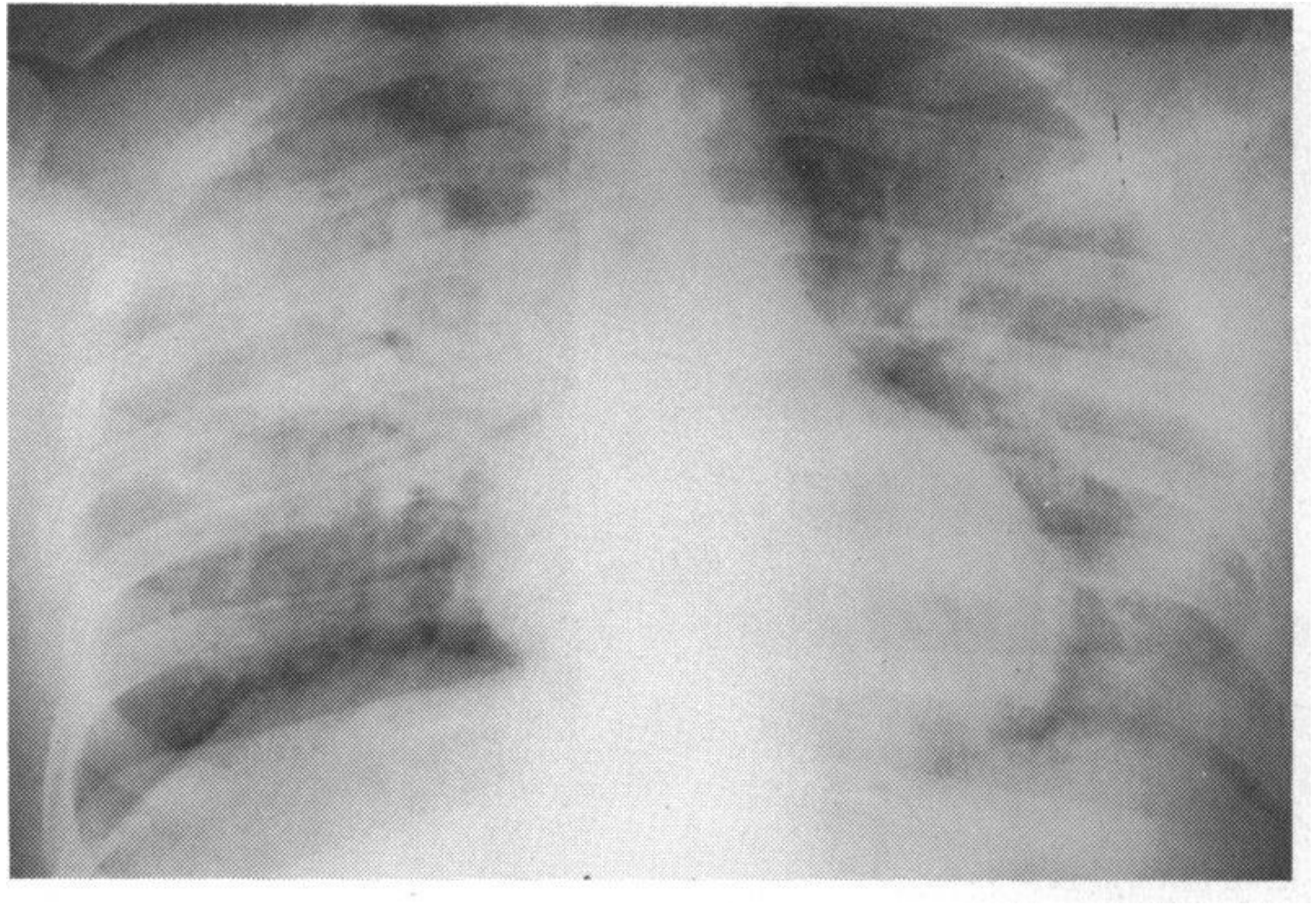
- Impaired consciousness
- Prostration, i.e., unable to sit, stand or walk without assistance
- Multiple convulsions: more than two episodes in 24 hours
- Acidotic breathing and respiratory distress
- Acute pulmonary oedema and acute respiratory distress syndrome
- Circulatory collapse or shock
- Anuria
- Jaundice
- Abnormal bleeding

Laboratory and other findings in severe malaria

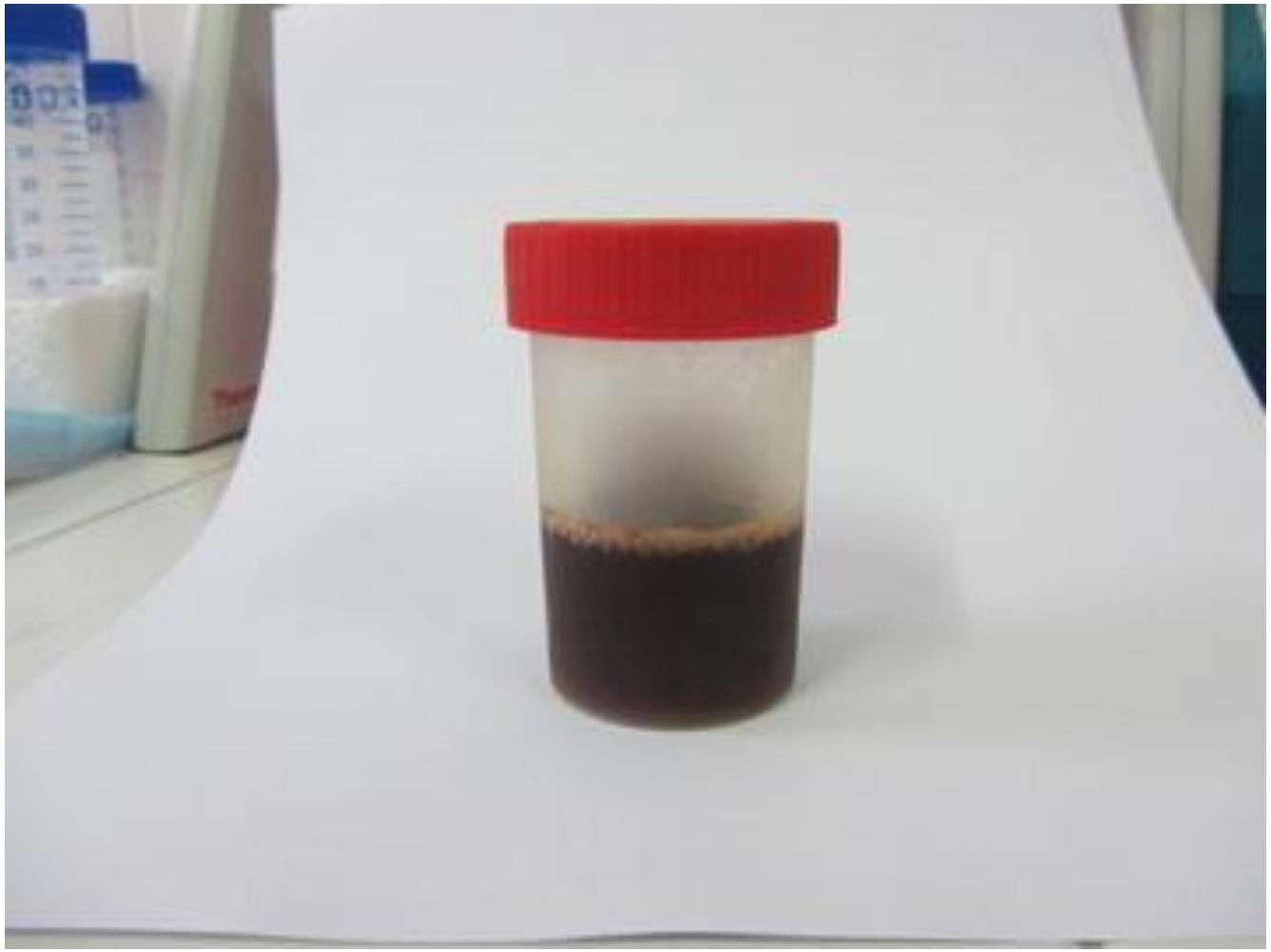
- Hypoglycaemia (< 2.2 mmol/l)
- Metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- Severe normocytic anaemia (< 7 g/dl)
- Hyperparasitaemia (> 2% in low-intensity transmission areas and >5% in areas with high stable malaria transmission) (WHO)
- Haemoglobinuria
- Hyperlactataemia (lactate >5 mmol/l)
- Renal impairment (serum creatinine >265 µmol/l)
- Pulmonary oedema (radiological)

** Thrombocytopenia is also a common feature of malaria due to all Plasmodium species, but in the absence of significant bleeding it is not regarded as a defining clinical manifestation of severe malaria*

Acute Pulmonary Edema in Falciparum Malaria

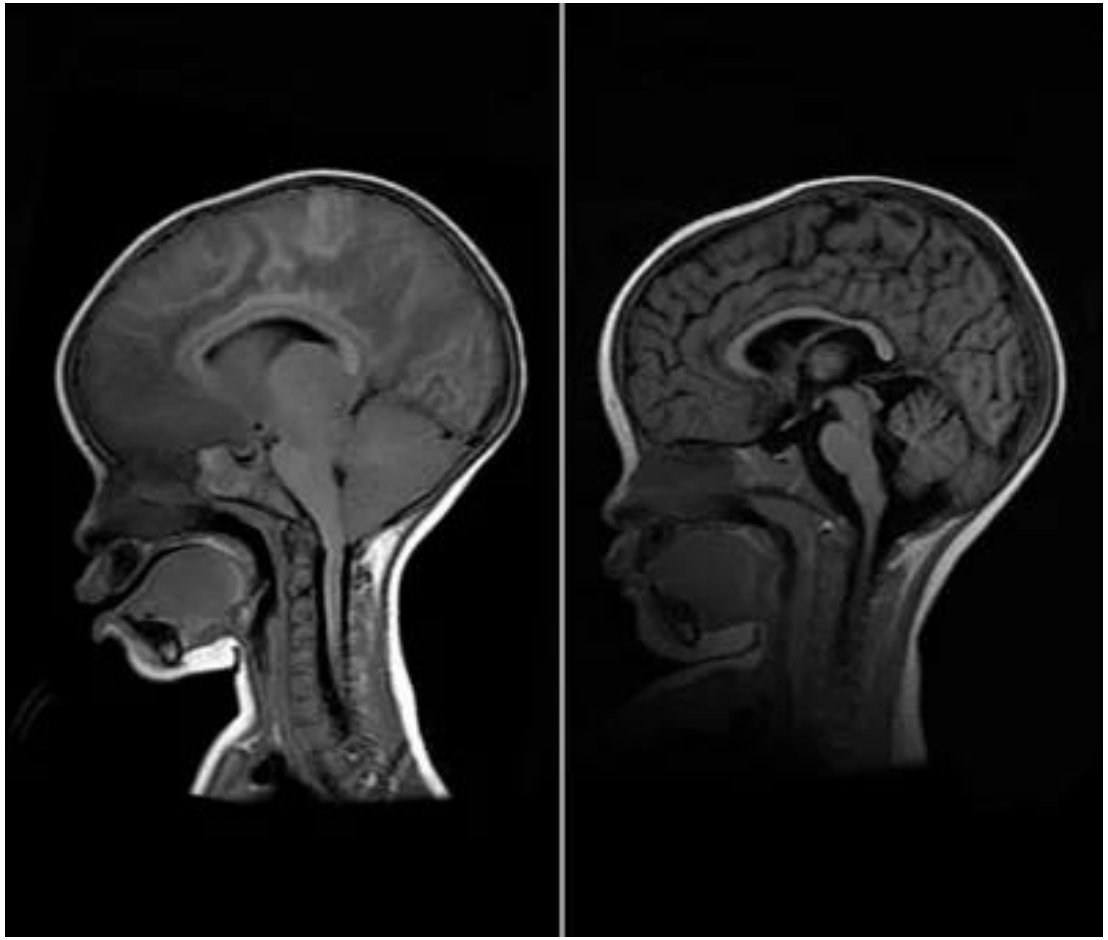


Hemoglobinuria due to severe intravascular hemolysis

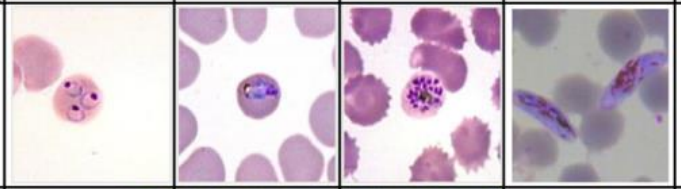
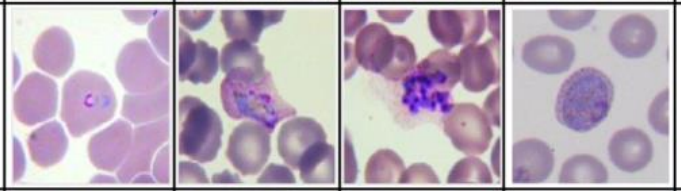
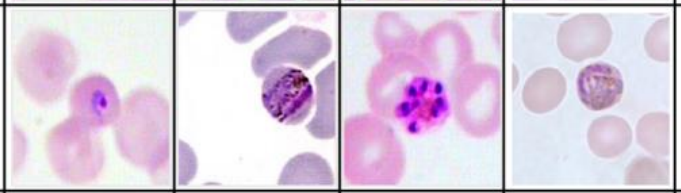
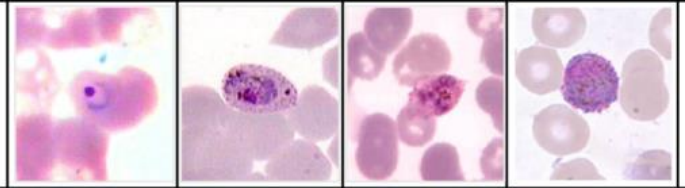
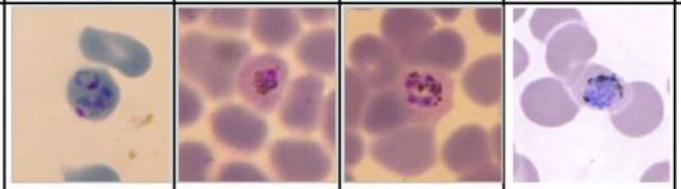


Malarial jaundice

Cerebral malaria



Different human Plasmodium species and their life cycles

Human Malaria					
Stages / Species	Ring	Trophozoite	Schizont	Gametocyte	
P. falciparum					• *Parasitised red cells (pRBCs) not enlarged.* • *RBCs containing mature trophozoites sequestered in deep vessels.* • *Total parasite biomass = circulating parasites + sequestered parasites.*
P. vivax					• *Parasites prefer young red cells* • *pRBCs enlarged.* • *Trophozoites are amoeboid in shape.* • *All stages present in peripheral blood.*
P. malariae					• *Parasites prefer old red cells.* • *pRBCs not enlarged.* • *Trophozoites tend to have a band shape.* • *All stages present in peripheral blood*
P. ovale					• *pRBCs slightly enlarged and have an oval shape, with tufted ends.* • *All stages present in peripheral blood.*
P. knowlesi					• *pRBCs not enlarged.* • *Trophozoites, pigment spreads inside cytoplasm, like P. malariae, band form may be seen* • *Multiple invasion & high parasitaemia can be seen like P. falciparum* • *All stages present in peripheral blood.*

Management of severe malaria at the PHC level

Any patient presenting with clinical features of severe malaria at a PHC or CHC **must be given pre-referral treatment and rapidly transferred** to the nearest hospital as an emergency (to reach the hospital within six hours of diagnosis).

Pre-transfer antimalarial drug treatment

If any significant delay (more than six hours) is expected in getting the patient from the PHC/CHC facility to treatment at the nearest hospital, give **one** of the following parenteral antimalarial drug treatments (if available):

- **IM artesunate** 2.4 mg/kg stat (off-label use), **or**
- **IM quinine** 20 mg salt/kg stat (divided into 10 mg/kg diluted to a concentration of 60-100 mg/mL administered into each anterior thigh).

Pre-transfer general management

- If **unconscious**, nurse the patient in the lateral or semi-prone position to **avoid aspiration**.
- Check blood glucose and **correct hypoglycemia** if present.
- If **hypotensive or in shock**, commence IV fluid resuscitation with normal saline.
- Overhydration may exacerbate ARDS.
- If in **respiratory distress**, administer oxygen.
- Reduce **high body temperature** (> 39°C) by administering paracetamol and fanning.
- **Control convulsions** with intravenous or rectal diazepam.
- **Convulsions may be due to hypoglycaemia**.

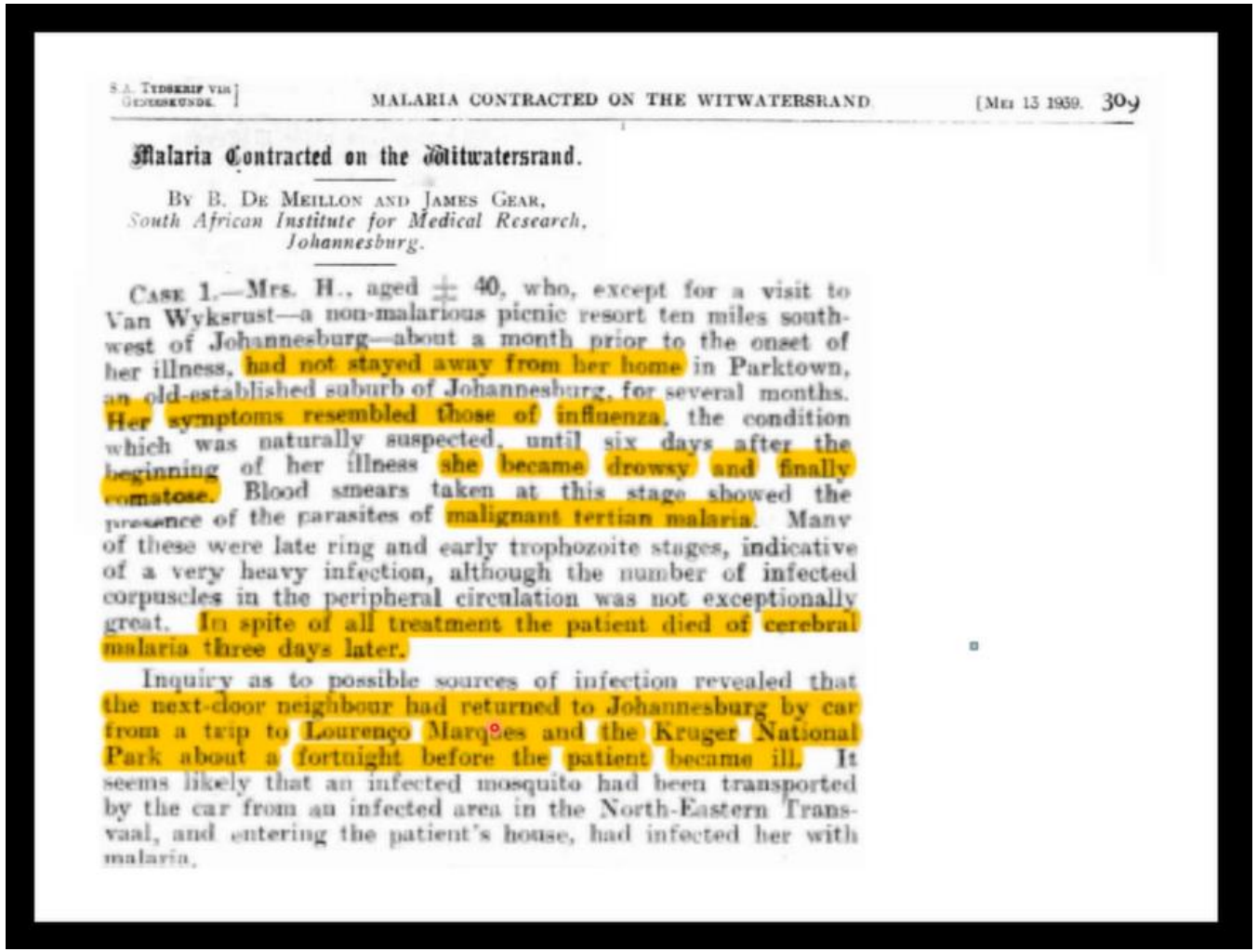
In-hospital care: Artesunate

- Patients **weighing >20 kg**: 2.4 mg/kg IV at 0, 12 and 24 hours then daily until patient is able to tolerate oral treatment.
- Children **weighing <20 kg**: 3 mg/kg IV at 0, 12 and 24 hours then daily until patient is able to tolerate oral treatment.
- Dissolve 60 mg artesunate powder in 1ml five per cent sodium bicarbonate solution (supplied with the artesunate powder) and **add 5ml five per cent dextrose** (or 0.9% sodium chloride) to give a solution of 10 mg/ml for injecting as a bolus into an IV cannula.
- Once reconstituted, artesunate solution is not stable and should be administered within 30 minutes; **solution not administered within 30 minutes should be discarded**.
- **At least three IV doses** (at 0, 12, and 24 hours) should be given for severe malaria before switching to oral therapy can be considered**.**
- **Can be safely administered during all trimesters of pregnancy.**
- **No change of dose required in renal failure.**
- **Can be given "push IVI" – no need to titrate, as is the case for Quinine**

Odyssean malaria

- Occasionally, infected mosquitoes are accidentally transported to non-endemic areas and transmit Odyssean (taxi/suitcase/airport) malaria.
- Gauteng, because of its large and mobile population, is most frequently affected, but Odyssean malaria can occur anywhere.
- The diagnosis is often delayed or missed, and there is a high rate of severe or fatal infection (case fatality rate 11% during the 2014 to 2016 period).
- Needlestick and transfusion or transplant-related malaria may occur unexpectedly, with similar poor outcomes.

First documented case in Johannesburg



S.A. Tydskrif vir Geneeskunde.] MALARIA CONTRACTED ON THE WITWATERSRAND [Mei 13 1939. 309

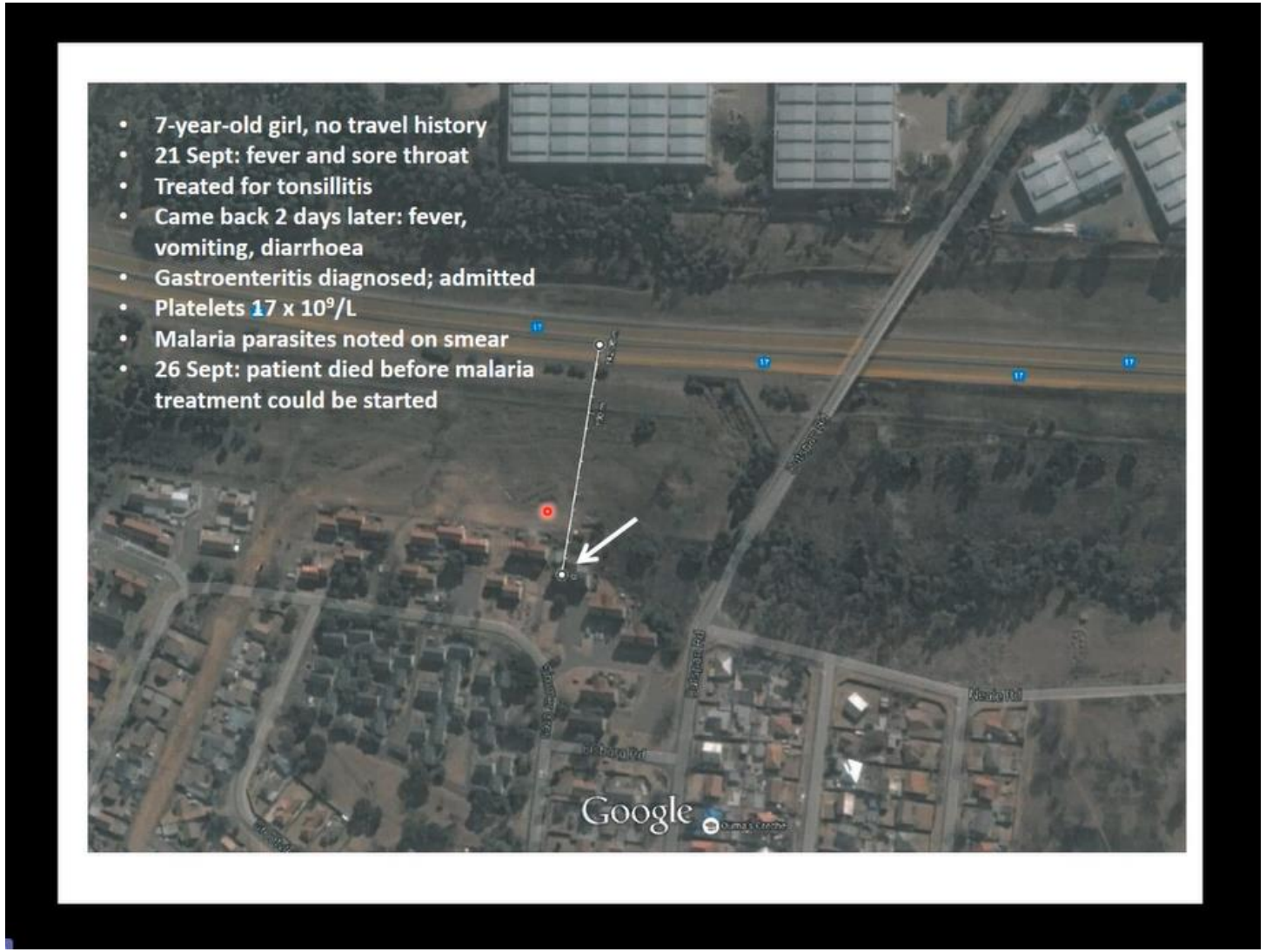
Malaria Contracted on the Witwatersrand.

By B. De Meillon and James Gear,
South African Institute for Medical Research, Johannesburg.

Case 1.—Mrs. H., aged ± 40, who, except for a visit to Van Wyksrust—a non-malarious picnic resort ten miles south-west of Johannesburg—about a month prior to the onset of her illness, had not stayed away from her home in Parktown, an old-established suburb of Johannesburg, for several months. Her symptoms resembled those of influenza, the condition which was naturally suspected, until six days after the beginning of her illness she became drowsy and finally comatose. Blood smears taken at this stage showed the presence of the parasites of malignant tertian malaria. Many of these were late ring and early trophozoite stages, indicative of a very heavy infection, although the number of infected corpuscles in the peripheral circulation was not exceptionally great. In spite of all treatment the patient died of cerebral malaria three days later.

Inquiry as to possible sources of infection revealed that the next-door neighbour had returned to Johannesburg by car from a trip to Lourenço Marques and the Kruger National Park about a fortnight before the patient became ill. It seems likely that an infected mosquito had been transported by the car from an infected area in the North-Eastern Transvaal, and entering the patient's house, had infected her with malaria.

Case study


7-year-old girl, no travel history
21 Sept: fever and sore throat
Treated for tonsillitis
Came back 2 days later: fever, vomiting, diarrhoea
Gastroenteritis diagnosed; admitted
Platelets 17 x 10^9/L
Malaria parasites noted on smear
26 Sept: patient died before malaria treatment could be started
Google

Odyssean Malaria cases in Johannesburg

Year	Cases	Deaths	CFR
1996-2004	46	6	13%
2007-2012	17	2	12%
2013	4		
2014	7	2	29%
2015	21	1	5%
2016	8	1	13%
2017	21	5	24%
2018	15	5	33%
2019	7	1	14%
2020	2	1	50%
2021	10		
2022	5	1	20%
Total	**163**	**25**	**15%**

* 10x the national case fatality rate

Malaria notification

- **The RAPID notification of all malaria cases in South Africa is mandatory**.
- Prompt notification of malaria cases to the local health authorities provides essential information needed for the Malaria Control Programmes to target their interventions efficiently and effectively.
- This is even more critical now that South Africa is working towards the ambitious target of malaria elimination. Wherever possible, mobile technology, such as Malaria Connect and the NMC APP, should be used to ensure notification within 24 hours to enable prompt response and follow-up by the Malaria Control Programme.
- The procedure for notifiable medical conditions is as follows:

  Malaria is a **category 1 notifiable medical condition** thus must be **reported/notified within 24 hours of diagnosis**.

  Comprehensive details of the new notification procedures are detailed in the **Standard Operating Procedures for Paper based reporting of Notifiable Medical Conditions (NMC)** via the NICD website www.nicd.ac.za

Electronic notification

- **Electronic notification via the NMC web or mobile APP** (from April 2018)
- Download the NMC APP at **https://mstrmobile.nicd.ac.za/nmc/** or your mobile APP Store or via the NICD website.
- Open the new case tab which contains the NMC case notification form and complete the required details.
- Upon completion, click save to save the captured details

Conclusion

- Travelers should be advised to use preventative strategies
- Offer chemoprophylaxis, when indicated
- Maintain a high index of suspicion, even without any travel history
- Odyssean malaria is a reality in Johannesburg
- Early diagnosis and treatment is key
- A negative rapid test does not exclude malaria
- Guard against sub-optimal treatment
- Identify severe malaria early, to prevent disease progression, death or disability
- Severe malaria cases should always be hospitalized
- Pre-transfer emergency care should be provided at PHC level
- Malaria is a notifiable condition

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Questions?

GAUTENG
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REPUBLIC OF SOUTH AFRICA

GGT2030
GROWING GAUTENG TOGETHER

Thank you

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