TREATMENT STRATEGIES TO COMBAT MALARIA

Charlotte Sriruttan-Nel
Pathologist
Centre for Emerging Zoonotic and Parasitic Diseases (CEZPD),
National Institute for Communicable Diseases (NICD)

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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

UNIVERSITEIT VAN PRETORIA
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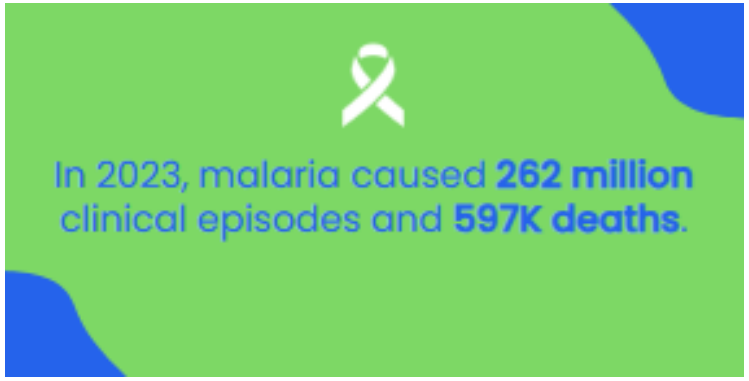
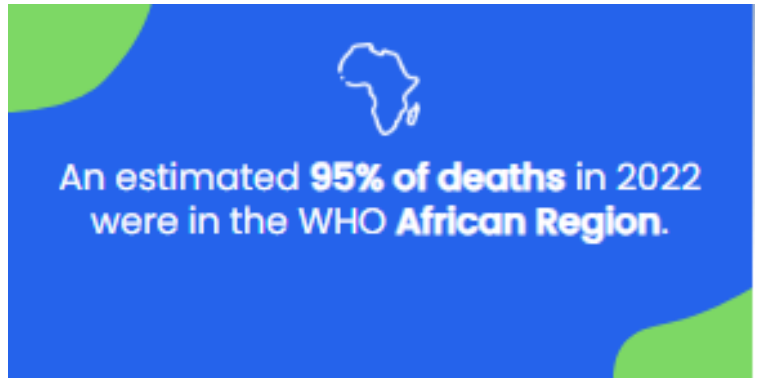
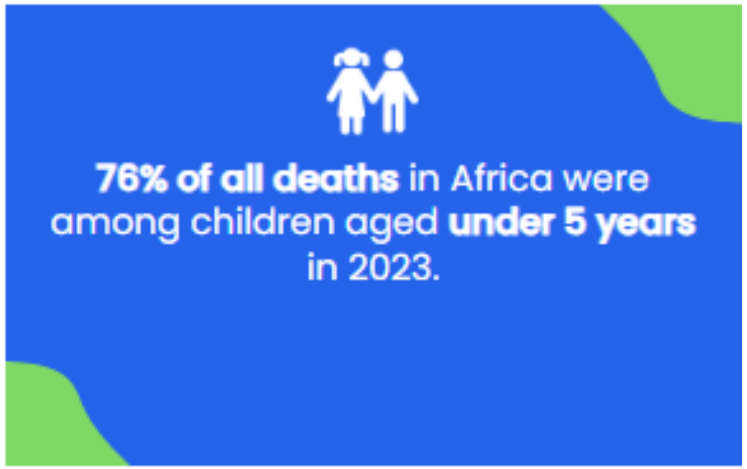
2030 NDP

30 YEARS OF FREEDOM
South Africa 1994 - 2024

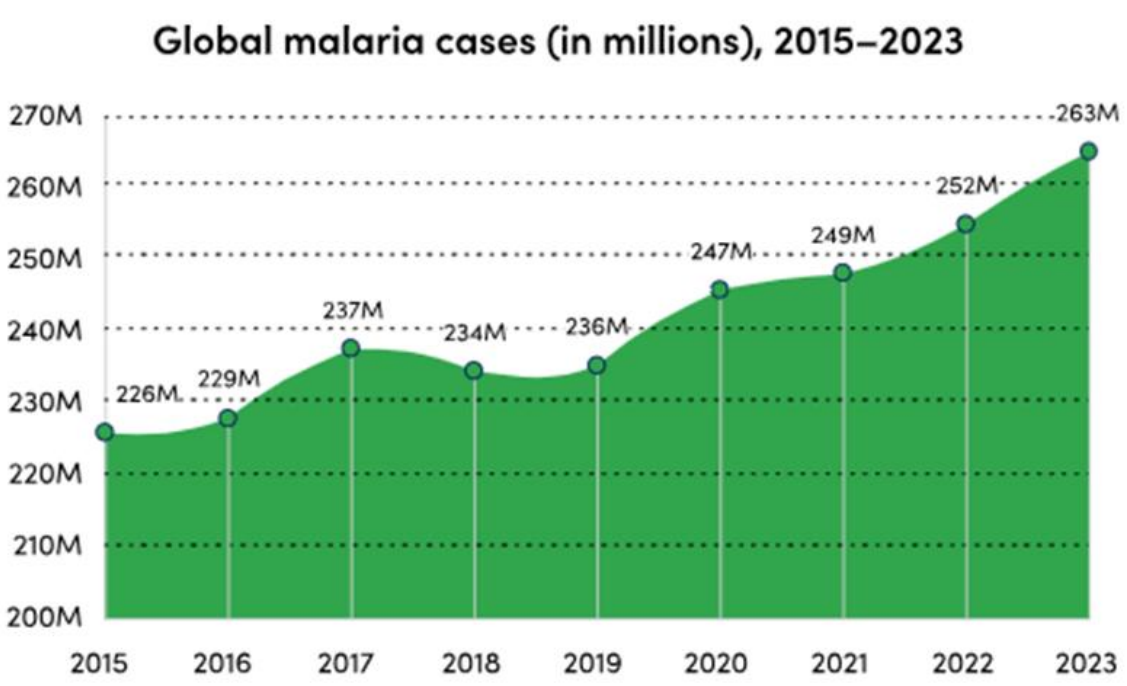
Global

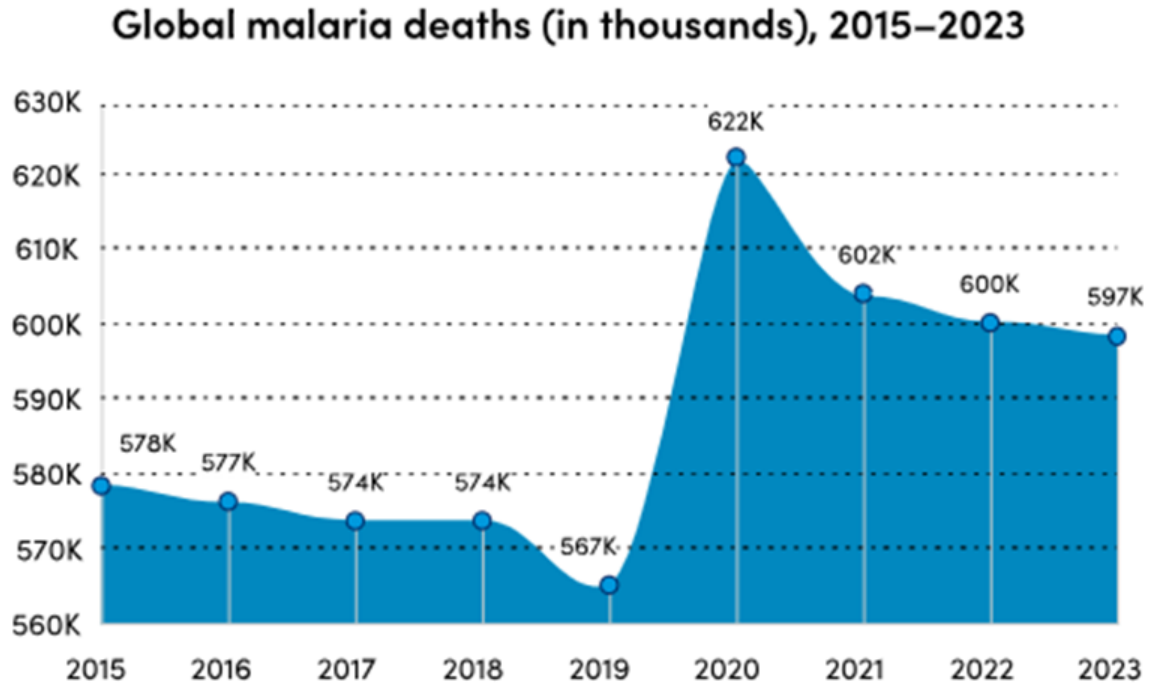






https://dashboards.endmalaria.org/en

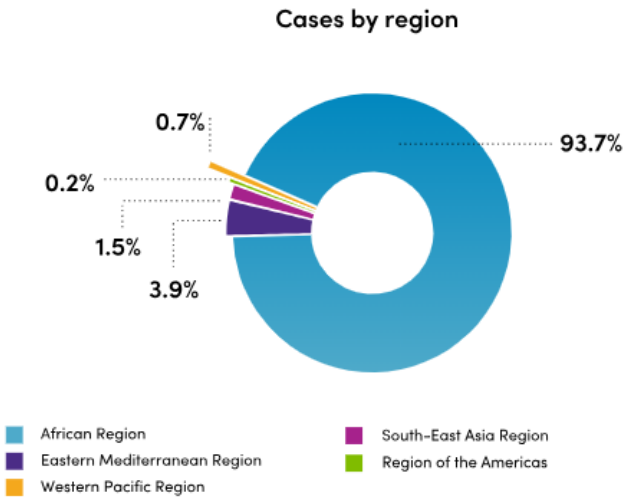


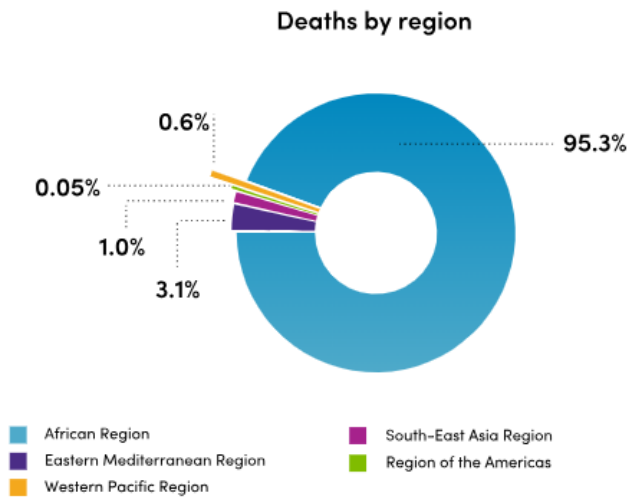


https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024

African Region

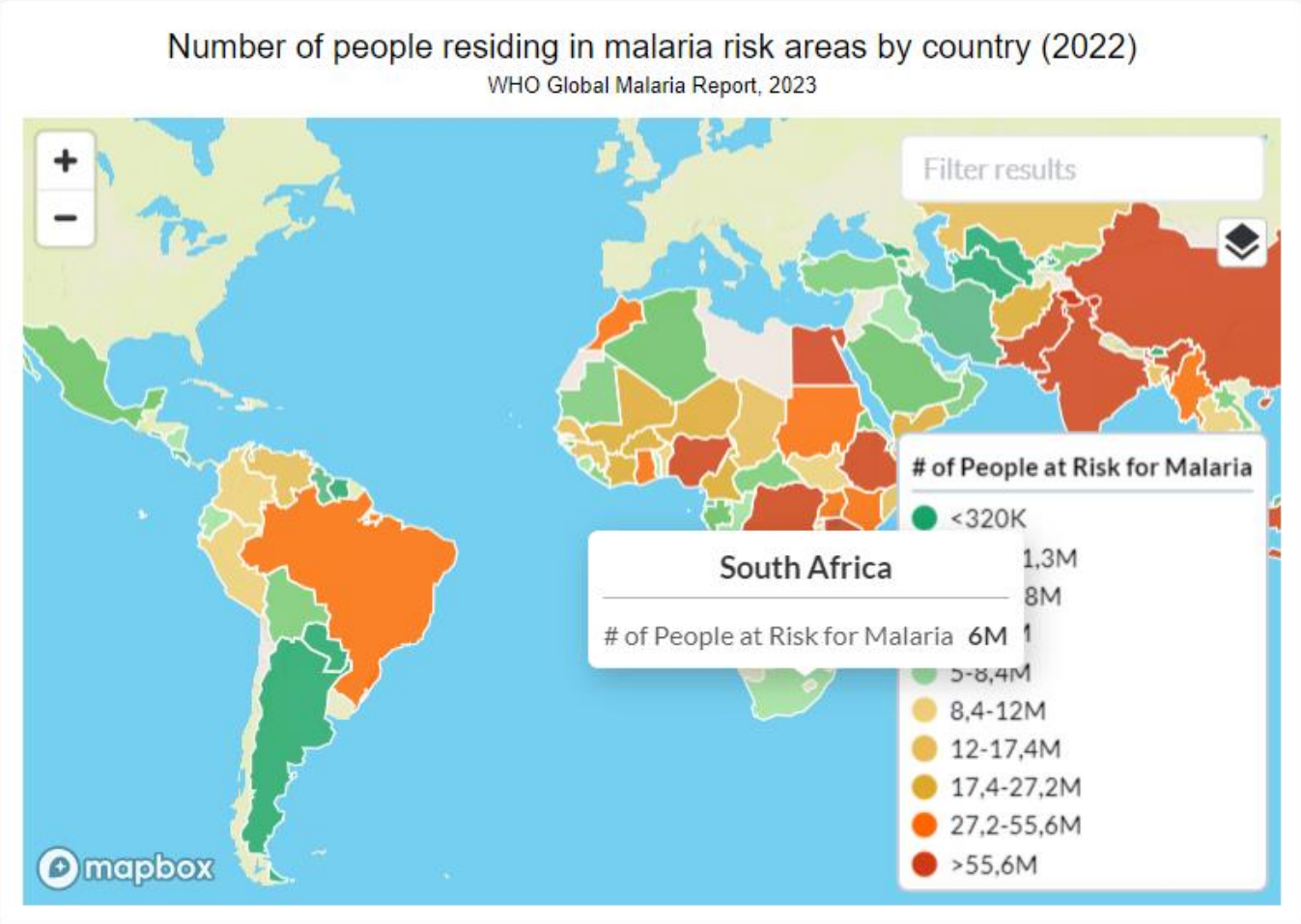
- The African Region bears the heaviest burden of malaria
  - accounting for an estimated 94% of global cases and
  - 95% of malaria-related deaths in 2023
- Five countries in the Region accounted for just over half of all malaria cases in 2023: Nigeria (25.9%), the Democratic Republic of the Congo (12.6%), Uganda (4.8%), Ethiopia (3.6%) and Mozambique (3.5%)

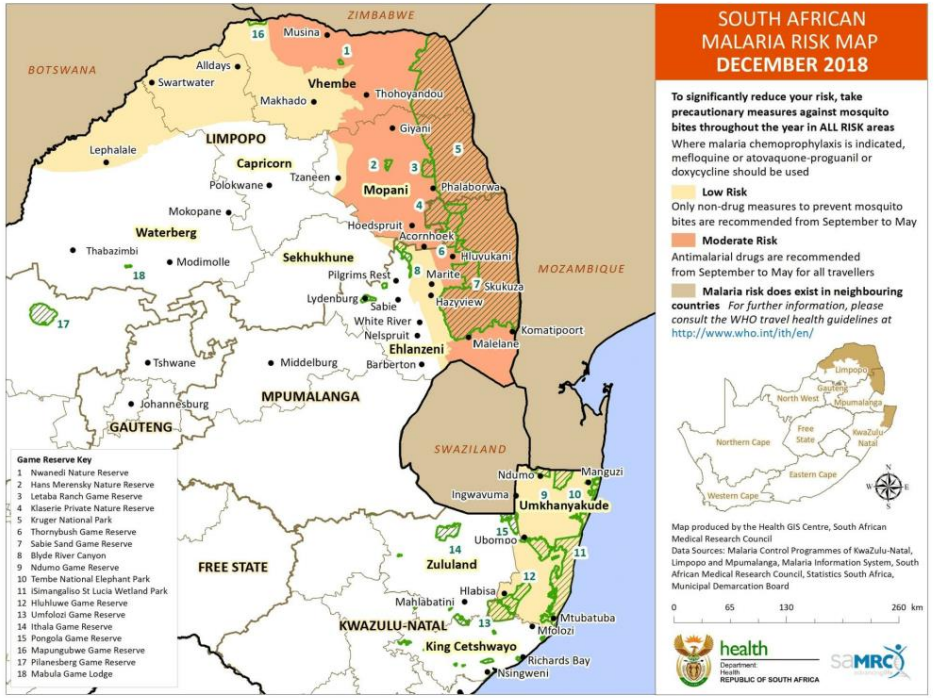




https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024

Southern Africa

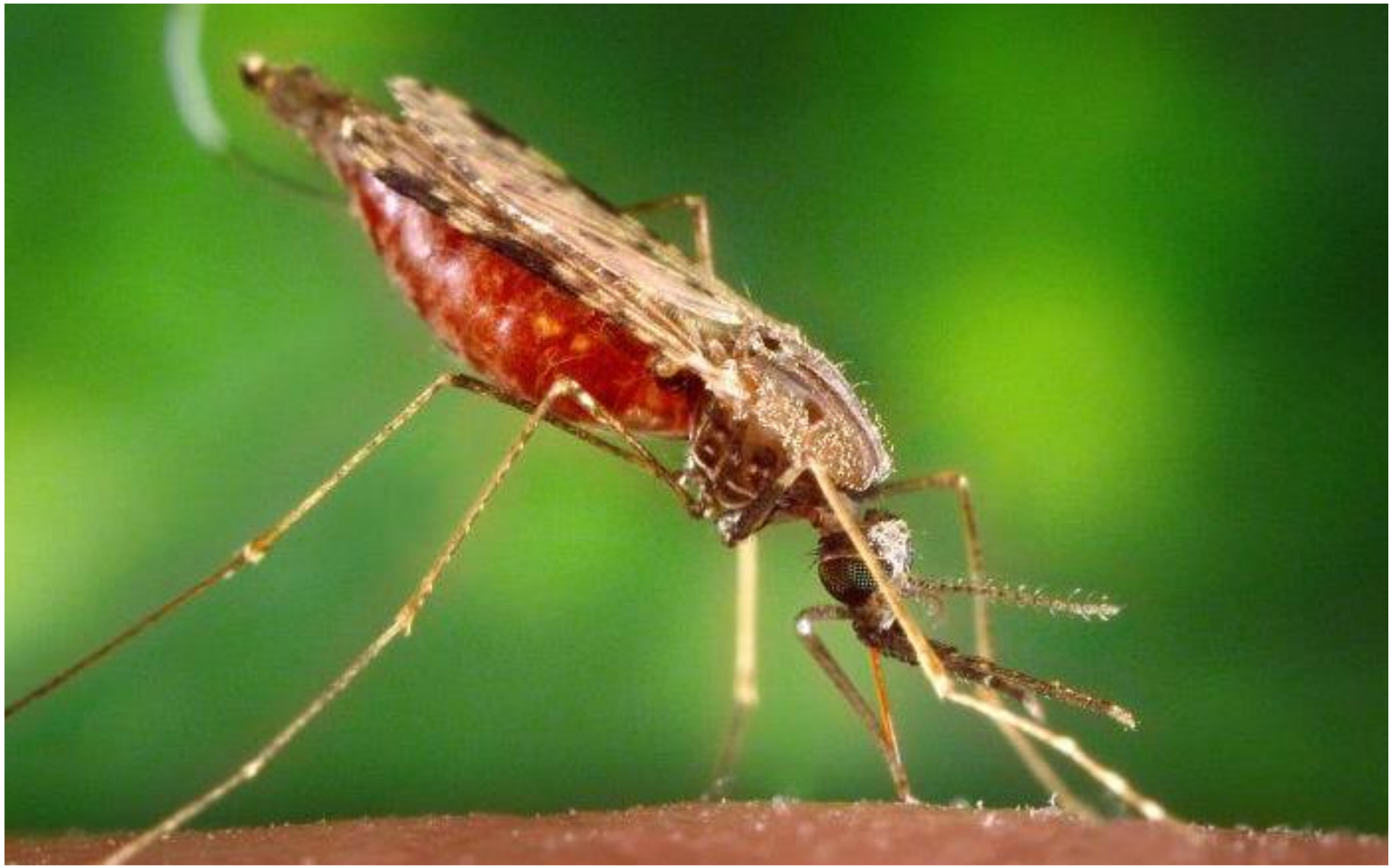


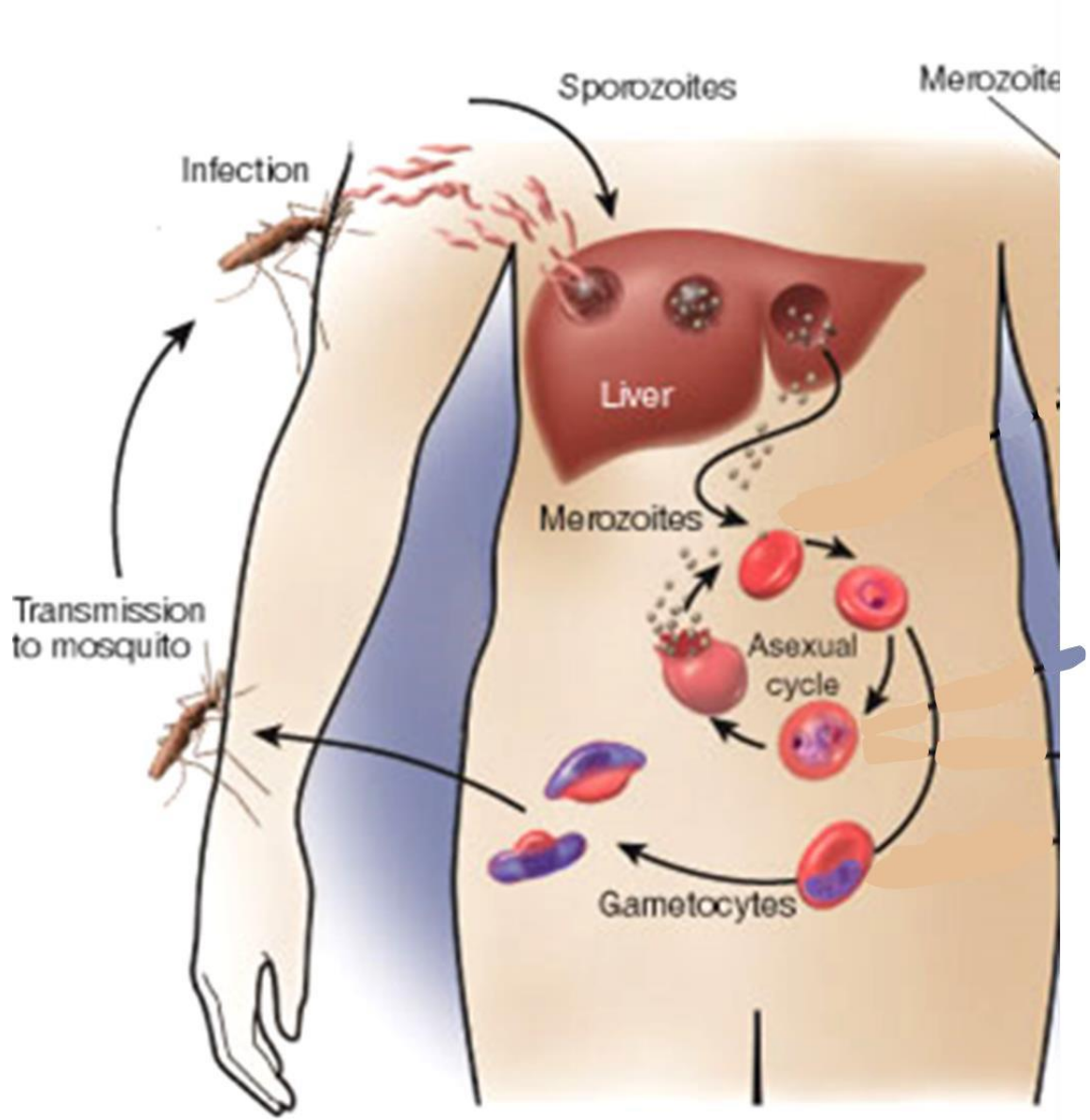


4 (+) SPECIES

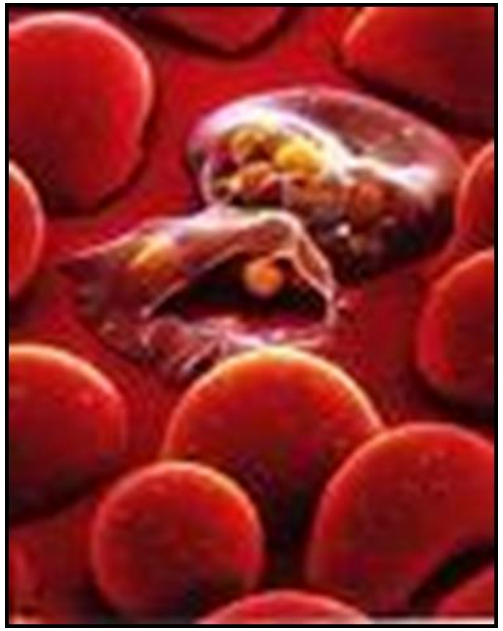
- *Plasmodium falciparum*
  - 95% of cases in southern Africa
  - most important species causing severe or fatal malaria
- *Plasmodium ovale*
- *Plasmodium vivax*
- *Plasmodium malariae*

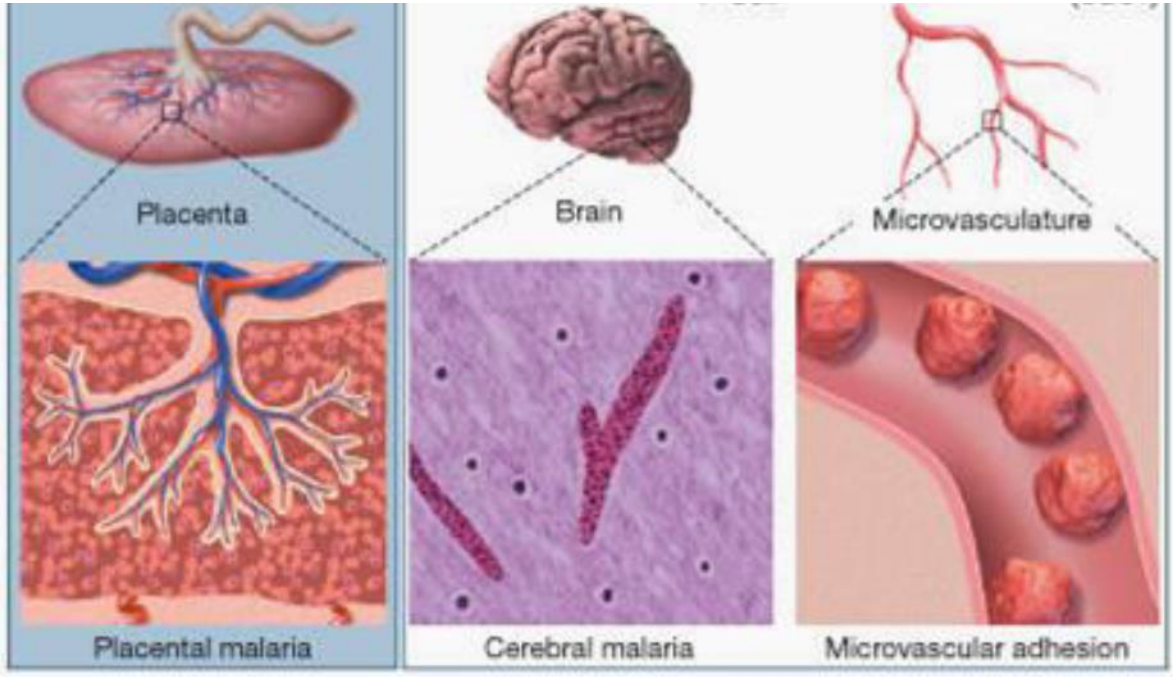
- *Plasmodium knowlesi*(only in SE Asia)
- *(P. simium, P. cynomolgi, P. brasilianum)*



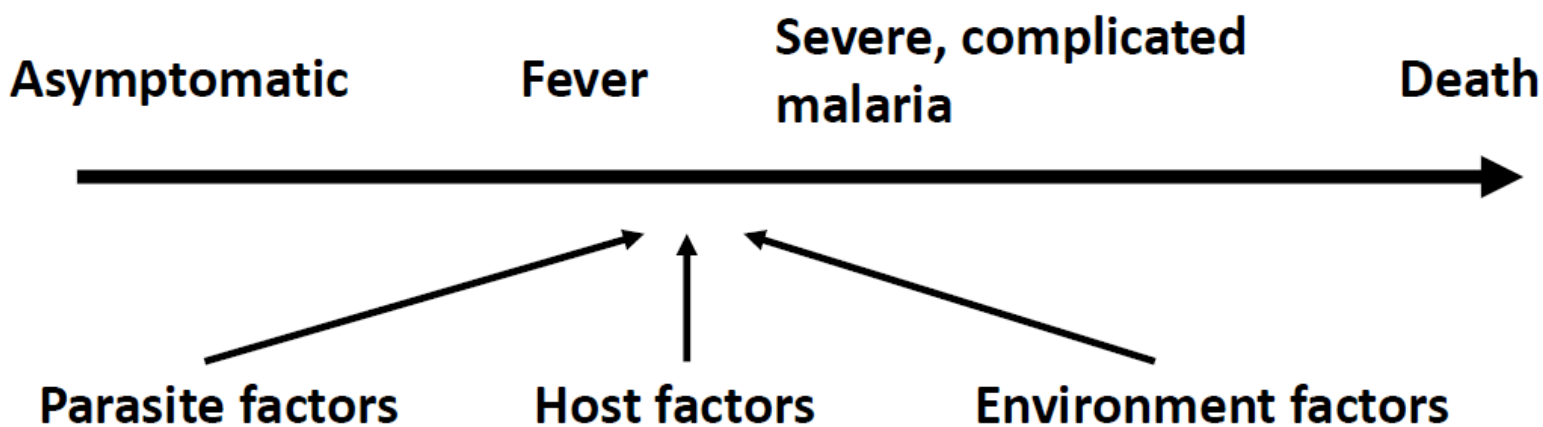

Sporozoites
Merozoite
Infection
Liver
Merozoites
Asexual
cycle
Transmission
to mosquito
Gametocytes

Pathogenesis of malaria





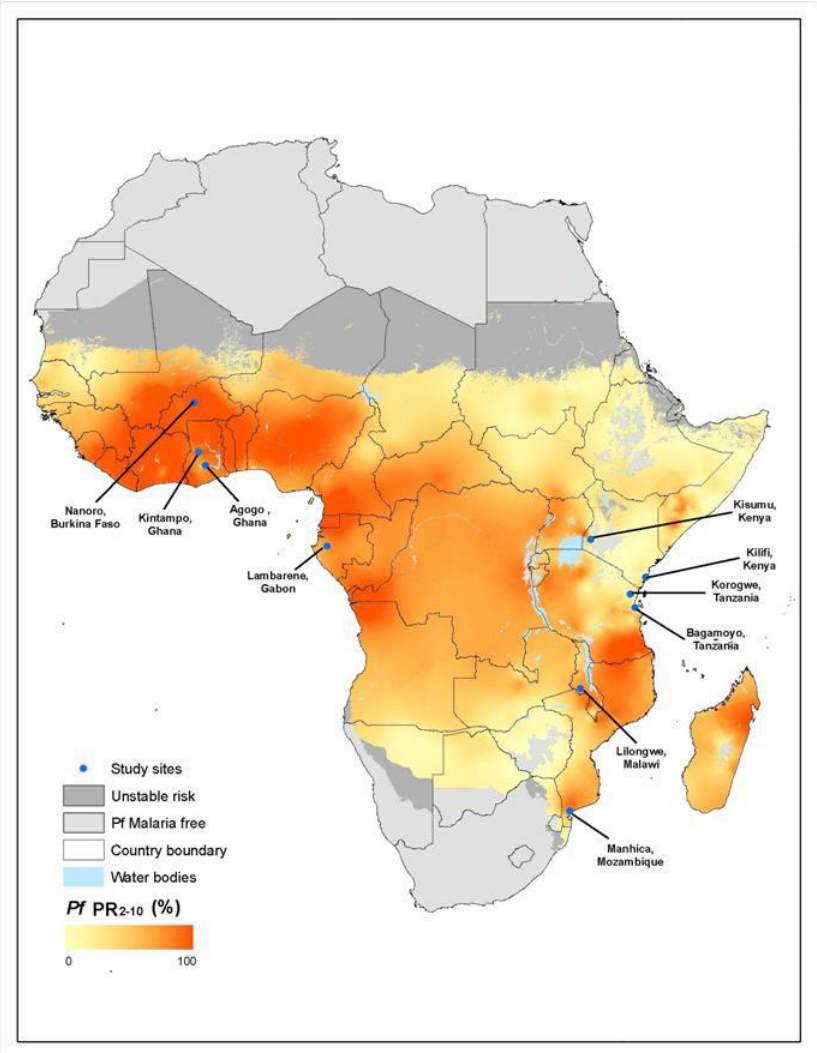
Outcome of malaria: interaction of many factors



Transmission scenarios

- **Stable transmission**:
  - prevalence of infection is high
  - high levels of population immunity develop

- **Unstable transmission**
  - population immunity is low
  - epidemics likely to occur



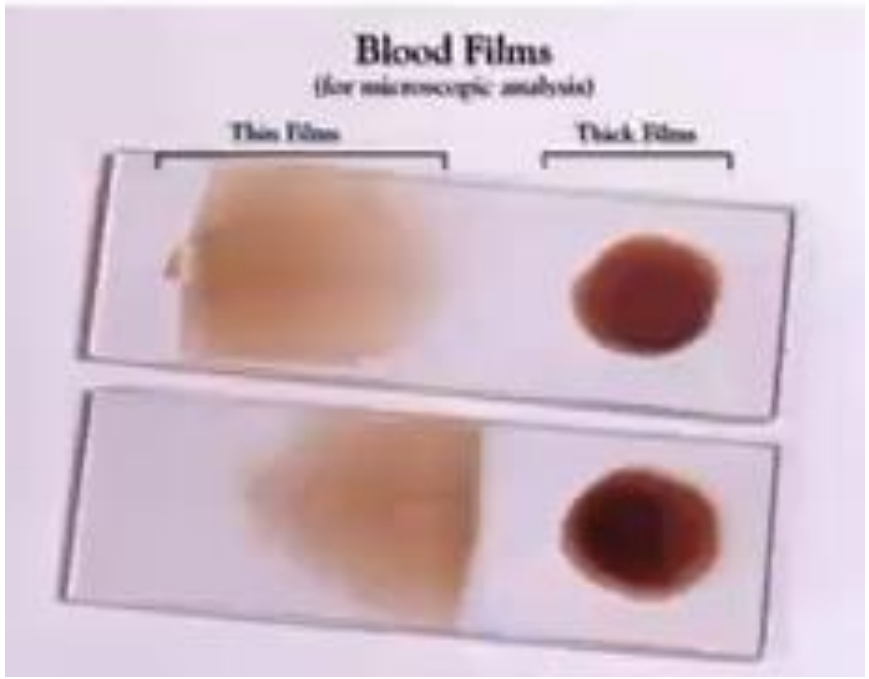
Management of malaria

- Malaria is preventable

- Malaria is treatable
  - diagnosis and management of malaria, especially falciparum malaria, is urgent
  - effective case management requires both early diagnosis and prompt treatment
  - high index of suspicion (acute febrile illness with history of travel to or resident in endemic areas)

Recommendations on malaria diagnosis

All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.
Both microscopy and RDTs should be supported by a quality assurance programme.
Good practice statement



Improving case management

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)

- Patients with suspected malaria should have parasitological confirmation of diagnosis with either microscopy or rapid diagnostic test (RDT) before antimalarial treatment is started

- Delayed diagnosis, underassessment of disease severity and inappropriate treatment are associated with significantly increased morbidity and mortality

Treatment aims

- The primary objective of treatment is **curing** the infection by ensuring the rapid and full elimination of *Plasmodium* parasites from a patient's bloodstream

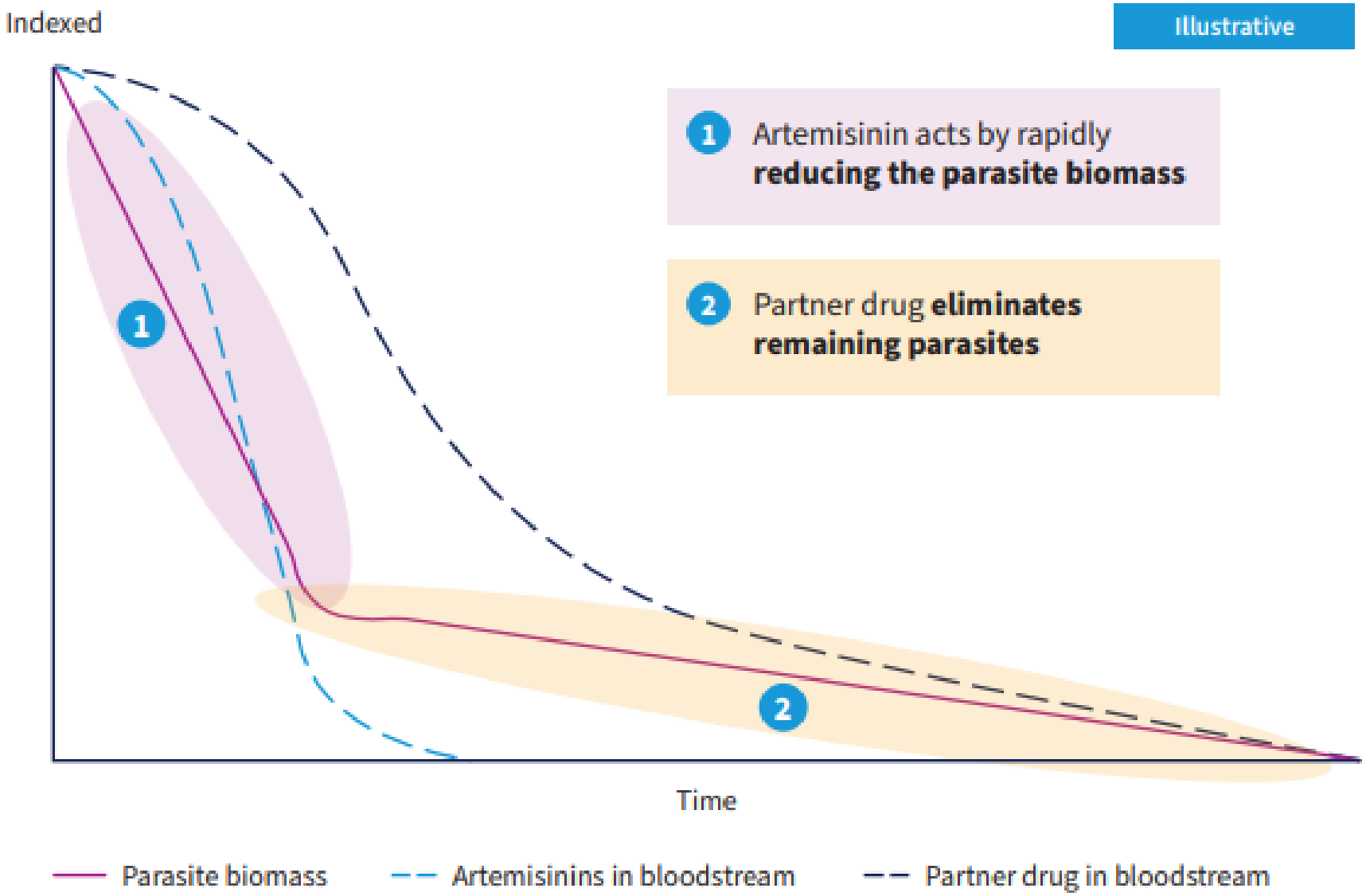
- This also **prevent** an uncomplicated case of malaria from progressing to severe disease or death

- From a public health perspective
- effective treatment also **minimises transmission** of the infection to others by reducing the infectious reservoir and
- by **preventing the emergence and spread of resistance** to antimalarial medicines

Artemisinin-based combination therapies (ACTs)

- Artemisinins: **established** anti-malarial agents with an **excellent safety profile**.
- **ACTs** recommended by the World Health Organization as **first-line treatment of uncomplicated falciparum malaria in all areas in which malaria is endemic since 2006**
- Replacing ineffective, failing treatments (chloroquine and sulfadoxine–pyrimethamine) with artemisinin-based combination therapies has **reduced the morbidity and mortality associated with malaria**
- Parenteral artesunate is indicated for treatment of severe malaria - in 2010, **parenteral artesunate was recommended as the first-line treatment for both paediatric and adult severe malaria** after large clinical trials showed the **significantly reduced mortality in patients** receiving artesunate compared with those receiving quinine

Figure 1. Evolution of parasite biomass in the body following ACT administration



Treating uncomplicated malaria

- Mild symptoms, are ambulant and have no evidence of organ dysfunction either clinically or on laboratory tests

- The recommended treatment
  - fixed dose artemisinin-based combination therapy (ACT), artemether-lumefantrine (Coartem®)
  - six doses administered over a three-day period
  - number of tablets per dose should be according to body weight

*For patients weighing more than 85 kg, advise extending the treatment course to FIVE days, administering FOUR tablets per dose, given twice daily for a total of 10 doses (off-label recommendation)

Treating severe malaria

- Medical emergency
- Highest level of care available
- Intravenous artesunate for at least 24 hours, followed by a full treatment course of artemether-lumefantrine as soon as the patient can tolerate oral treatment

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:

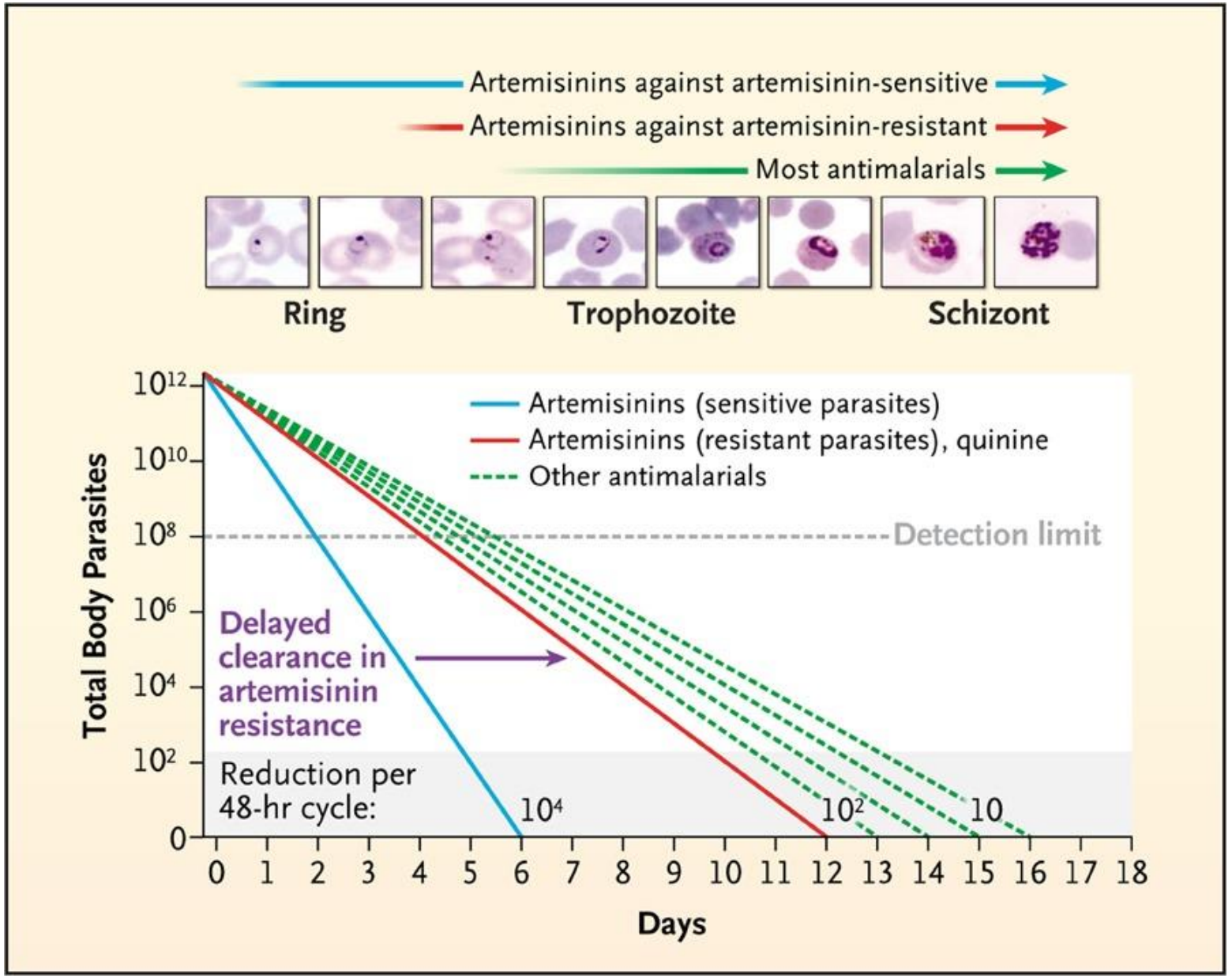
- hypoglycaemia (<2.2mmol/l or <40mg/dl)
- metabolic acidosis (plasma bicarbonate <15mmol/l)
- severe normocytic anaemia (<7g/dl)
- hyperparasitaemia
- haemoglobinuria
- hyperlactataemia (lactate >5mmol/l);
- renal impairment (serum creatinine >265µmol/l)
- pulmonary oedema (radiological)

Other strategies

- Reducing the transmissibility of treated *P. falciparum* infections in areas of low intensity transmission

  - Primaquine effective against mature gametocytes
  - adding a **single low dose** of 0.25 mg/kg to full artemether-lumefantrine treatment to patients with *P. falciparum* malaria to further reduce malaria transmission
  - Implemented as part of elimination strategy

Antimalarial drug resistance



N Engl J Med 2011; 365:1073-1075

Repeated malaria episodes

RECURRENCE:

Symptoms of malaria can recur after varying symptom-free periods.

Depending upon the cause, recurrence can be classified as either or reinfection, relapse or recrudescence.

- **Reinfection** = Reinfection is an infection acquired from a new mosquito bite
- **Relapse** is recurrence of disease after it has been apparently cured. In malaria, true relapses are caused by reactivation of dormant liver stage parasites (hypnozoites) found in *P. vivax* and *P. ovale*
- **Recrudescence** is when symptoms return after a symptom-free period. It is caused by parasites surviving in the blood as a result of inadequate or ineffective treatment.

Reasons for treatment failure

- Appropriate drug? [NB relapsing malaria]
- Dosage?
- Dosing intervals, duration?
- Absorption issues – vomiting?
- Dosage adjusted for age and weight?
- Co-administration of food i.e. fat for Coartem?
- Compliance?
- Product quality – counterfeit, fake, expired?
- Parasite drug resistance?

Genomic surveillance in SA

Very low prevalence of validated *kelch13* mutations and absence of *hrp2/3* double gene deletions in South African malaria-eliminating districts (2022-2024)

Jaishree Raman, Maxwell Mabona, Qedusizi Nyawo, Brighton Mangena, Gerdalize Kok, Lihle Mathaba, Gillian Malatje, Sonja B Lauterbach, Takalani I Makhanthisa, Hazel Gwarinda, Blaženka D Letinić, Arinao Ndadza, Eric Raswiswi, Mbavhalelo Shandukani, Ednah Baloyi, Ziyanda Fekema, Arshad Ismail, Jonathan Featherston, Bryan Greenhouse, Jennifer L Smith, Andres Aranda-Diaz

doi: https://doi.org/10.1101/2025.03.31.25324948

- findings suggest that the recommended treatments and diagnostics in South Africa are effective
- strong selection for antimalarial drug resistance markers across southern Africa combined with high regional interconnectedness, emphasizes the need for sustained malaria molecular surveillance to support South and southern Africa achieve their elimination goals

Strategies for antimalarial resistance

Four pillars of the "Strategy to respond to antimalarial drug resistance in Africa"

1. Strengthen surveillance of antimalarial drug efficacy and resistance.
2. Optimize and better regulate the use of diagnostics and therapeutics to limit drug pressure through pre-emptive measures.
3. React to resistance by limiting the spread of antimalarial drug-resistant parasites.
4. Stimulate research and innovation to better leverage existing tools and to develop new tools against antimalarial drug resistance.

Multiple first-line therapies as part of the response to antimalarial drug resistance

An implementation guide

World Health Organization

Kokori *et al. Malaria Journal* (2024) 23:25
https://doi.org/10.1186/s12936-024-04844-y

Malaria Journal

REVIEW Open Access

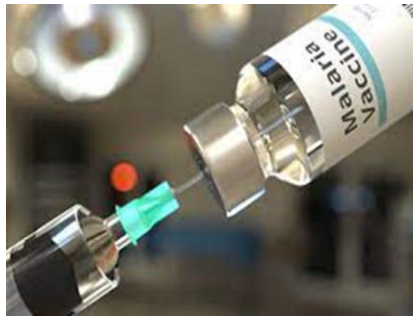
Triple artemisinin-based combination therapy (TACT): advancing malaria control and eradication efforts

Emmanuel Kokori[1], Gbolahan Olatunji[1], Adeola Akinboade[1], Aminat Akinoso[1], Emmanuel Egbunu[2], Sikiru Ademola Aremu[3], Chuka Emmanuel Okafor[4], Olamide Oluwole[3] and Nicholas Aderinto[5*]

Preclinical exploratory	Human volunteers	Patient exploratory	Approved
TCP-1			
• SC83288 • GSK484 • IWY357 • S011-1793	• GSK701 • MMV688533 • INE963	• SJ733 • ZY-19489 + ferroquine	• Arterolane (OZ277) • Artesunate • Artemether • Dihydroartemisinin • Chloroquine • Piperaquine • Amodiaquine • Pyronaridine • Lumefantrine • Mefloquine • Quinine
TCP-1,4			
• MMV371 • ELQ-331			• Atovaquone • Pyrimethamine • Sulfadoxine • Proguanil
TCP-1,5			
• MMV693183 • MMV1793609		• Cipargamin	
TCP-1,4,5			
• WM382 • BRD5018		• M5717 + pyronaridine • Ganaplacide + lumefantrine	
TCP-3,4			
			• Tafenoquine • Primaquine
TCP-5			
• TB-31F			• Primaquine (single, low dose)
TCP-6			
• Lotilaner • Isoxazolines			
Sporozoite			
• MAM01 (ATRC-501)		• L9LS • CIS43LS	
Immunomodulator			
	• Ruxolitinib		

VACCINES

- Two malaria vaccines, RTS,S/AS01 (RTS,S) and R21/Matrix-M, are now recommended by WHO for use in malaria endemic areas
- Between 2019 and 2023, approximately 2 million children in Ghana, Kenya and Malawi received the RTS,S vaccine
- An evaluation of impact demonstrated a 13% reduction in all-cause mortality and a 22% reduction in hospitalizations of severe malaria among children age-eligible for vaccination during this period
- By early December 2024, a total of 17 countries had introduced the vaccine through routine childhood immunization



Parasitology Laboratory

Dr Charlotte Sriruttan-Nel

Email: charlottes@nicd.ac.za

Vector Control Laboratory

Prof Basil Brooke

Email: basilb@nicd.ac.za

Antimalarial Resistance Monitoring Laboratory

Dr Jaishree Raman

Email: jaishreer@nicd.ac.za

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