

Parasitic Diseases: Malaria and Leishmaniasis

Russell Lewis

Associate Professor, Infectious Diseases
Department of Molecular Medicine

MEP 2491 Infectious Diseases
2 May 2023



UNIVERSITÀ
DEGLI STUDI
DI PADOVA

Protozoa “first animals”

Means of spread	Habitat	Intracellular
	Extracellular	
Insect-borne*	African trypanosome (blood)	<i>Plasmodium</i> (liver, red blood cells) <i>Leishmania</i> (macrophage) South-America trypanosome (macrophage, muscle, nerve)
Water-born	Amoeba (gut) <i>Giardia</i> (gut) <i>Cryptosporidium</i> (gut) <i>Isospora</i> (gut) <i>Trichomonas</i> (urogenital)	Toxoplasma (macrophage)

The protozoa carried by insect vectors are mainly confined to tropics by the distribution of the vectors

World Malaria Day



Health Topics ▾

Countries ▾

Newsroom ▾

Emergencies ▾

Data ▾

About WHO ▾



619 000
malaria deaths
in 2021



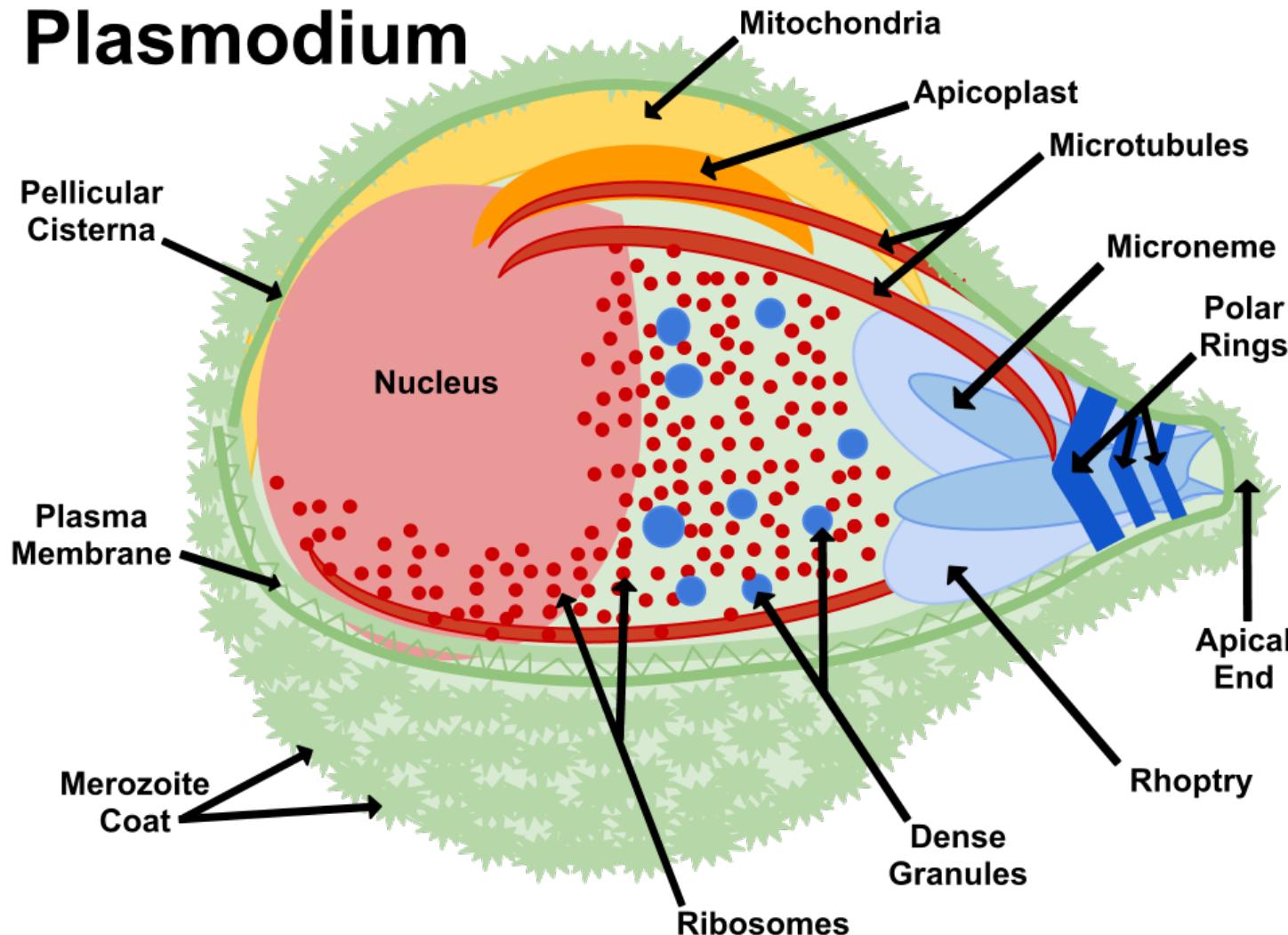
247 million
new cases of malaria
in 2021



95%
of all malaria cases
are in WHO African Region

The pathogen

Plasmodium



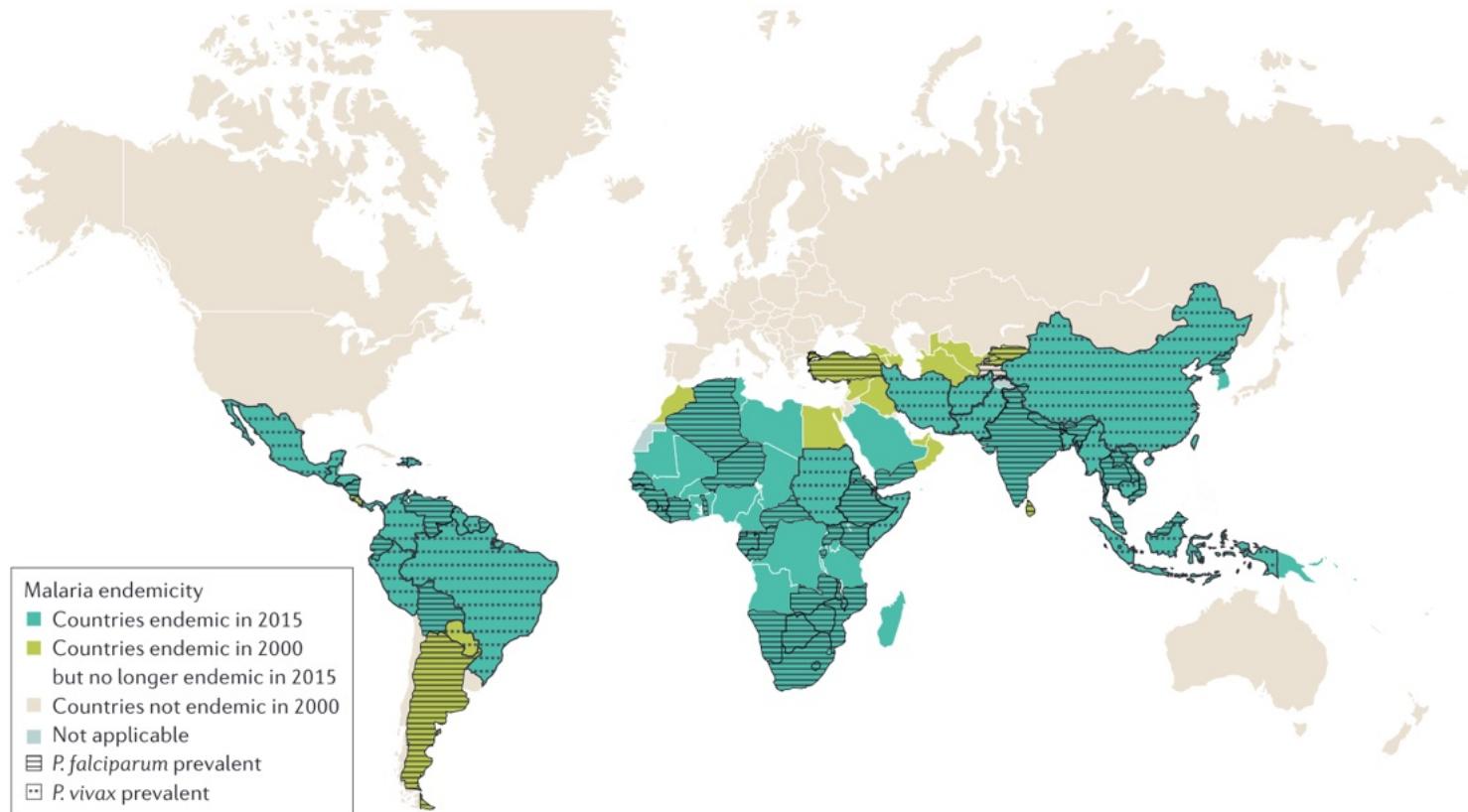
Apicomplexa group of protozoa- specialized complex of apical organelles (micronemes, rhoptries, dense granules) involved in host invasion

The vector



Malaria is transmitted by the bite of *Plasmodium*-infected female mosquitoes of the *Anopheles* genus

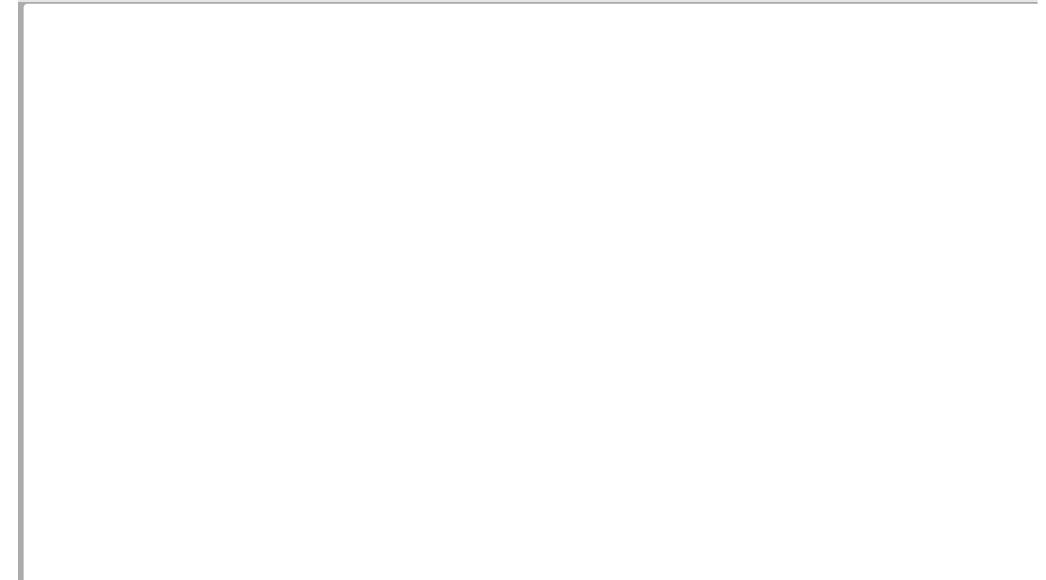
Malaria endemic regions



The impact of malaria on humans is staggering

- Kills roughly 2000 people per day, most of whom are children in Africa
- The strongest documented force for evolutionary selection in the recent history of the human genome
 - Malaria is the evolutionary driving force behind the most common Mendelian diseases of humankind: sickle-cell disease, thalassemia, glucose-6-phosphatase deficiency, and other erythrocyte defects
- Malaria was once prevalent throughout much of the inhabited world, but has been eliminated from the USA and Canada, Europe, and Russia (chloroquine-based treatment, large-scale insecticide using DDT)
 - Malaria prevalence resurged in tropical countries from the 1970s to the 1990s because of a combination of relaxation of control efforts, increasing antimalarial drug resistance, and insecticide resistance in the mosquito vectors
 - More selective vector control approaches (insecticide bed nets, indoor residual spraying) and the introduction of artemisinin-based regimens have led to an overall reduction in mortality in the last 20 years
- Growing resistance to insecticides in mosquitoes (*Anopheles gambiae*)

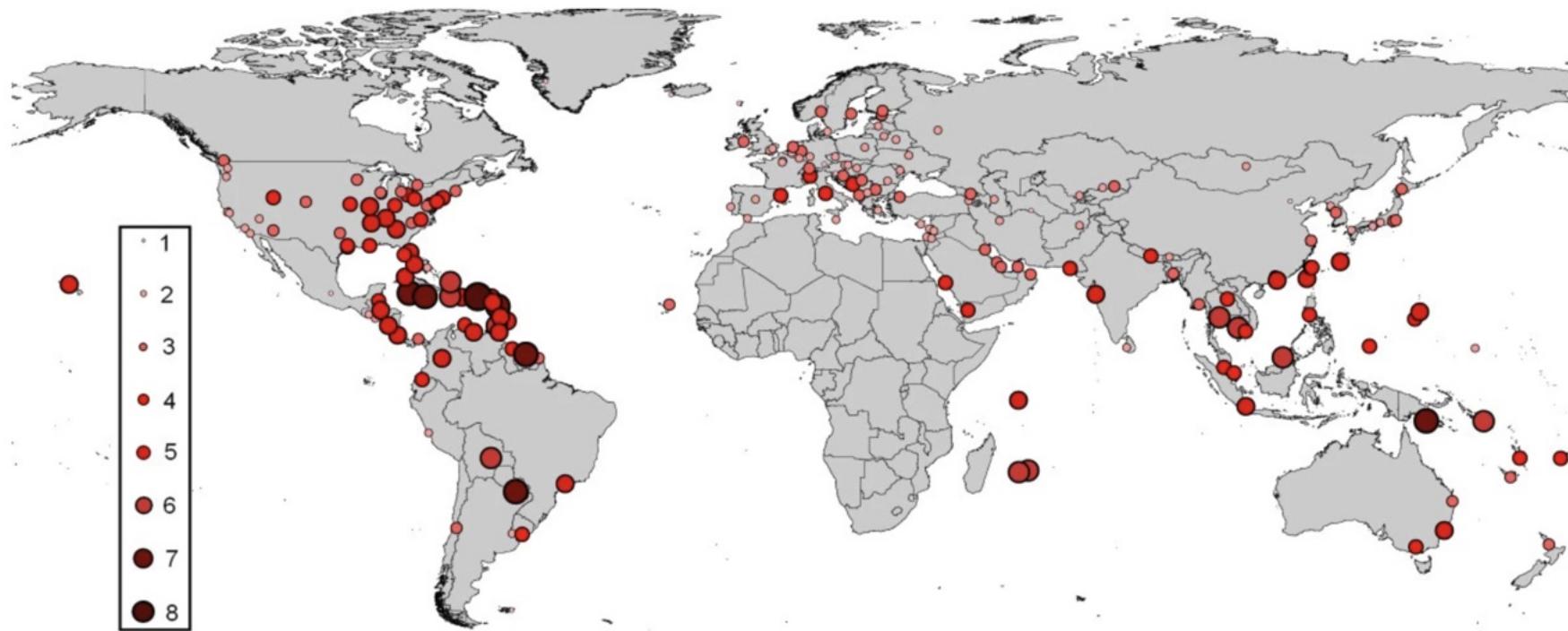
Trends in Malaria death rates in 2021



Malaria deaths by age

Airport or “suitcase-associated” malaria

From: [Estimating the malaria risk of African mosquito movement by air travel](#)



(Tatem et al., 2006)

Autochthonous transmission

- Airport malaria
- Asymptomatic donors from endemic areas with low-level parasitaemia
 - Blood donors
 - Solid organ transplant

Cases in Italy

Rare malaria death of girl in northern Italy puzzles doctors

⌚ 5 September 2017

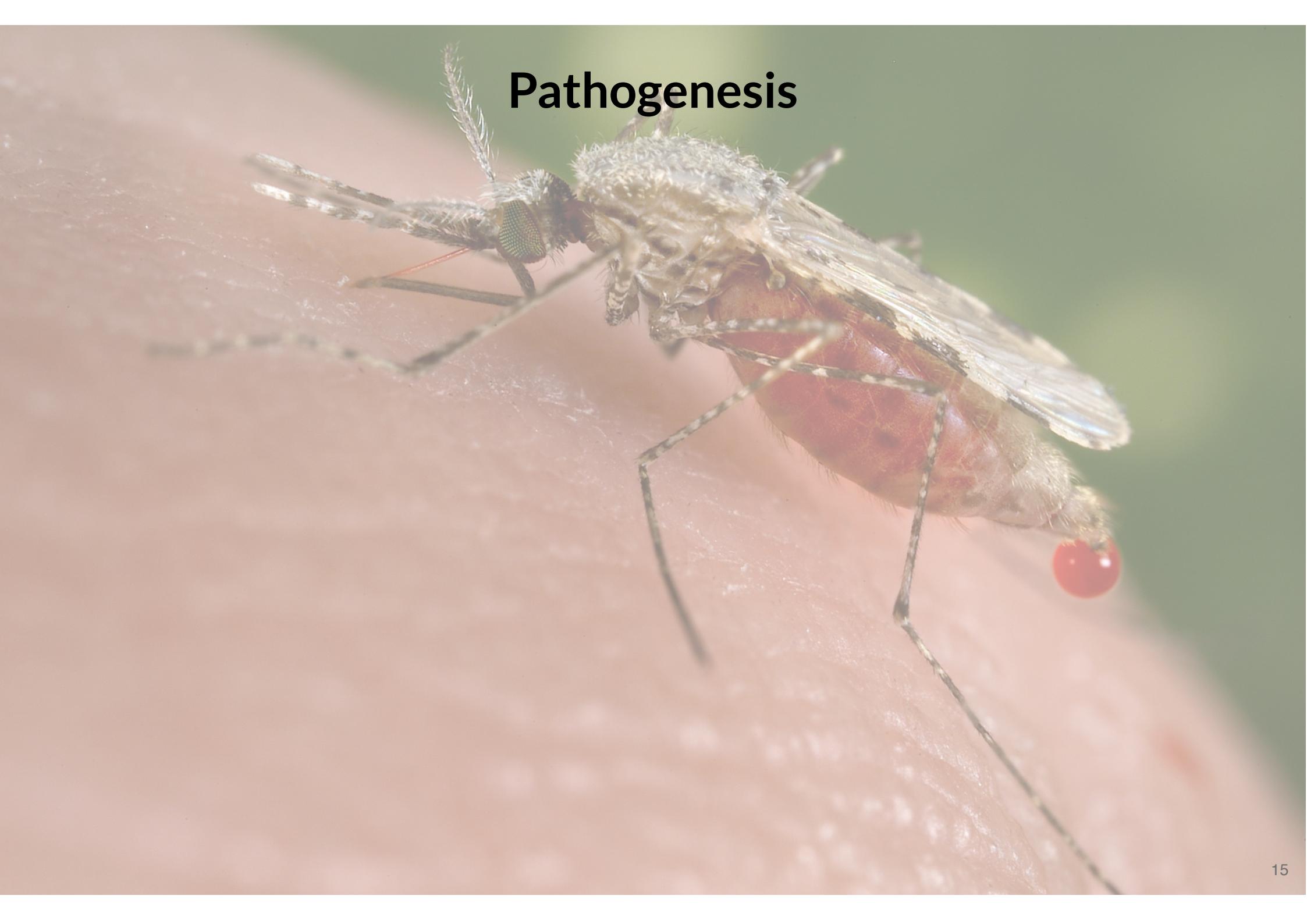


SCIENCE PHOTO LIBRARY

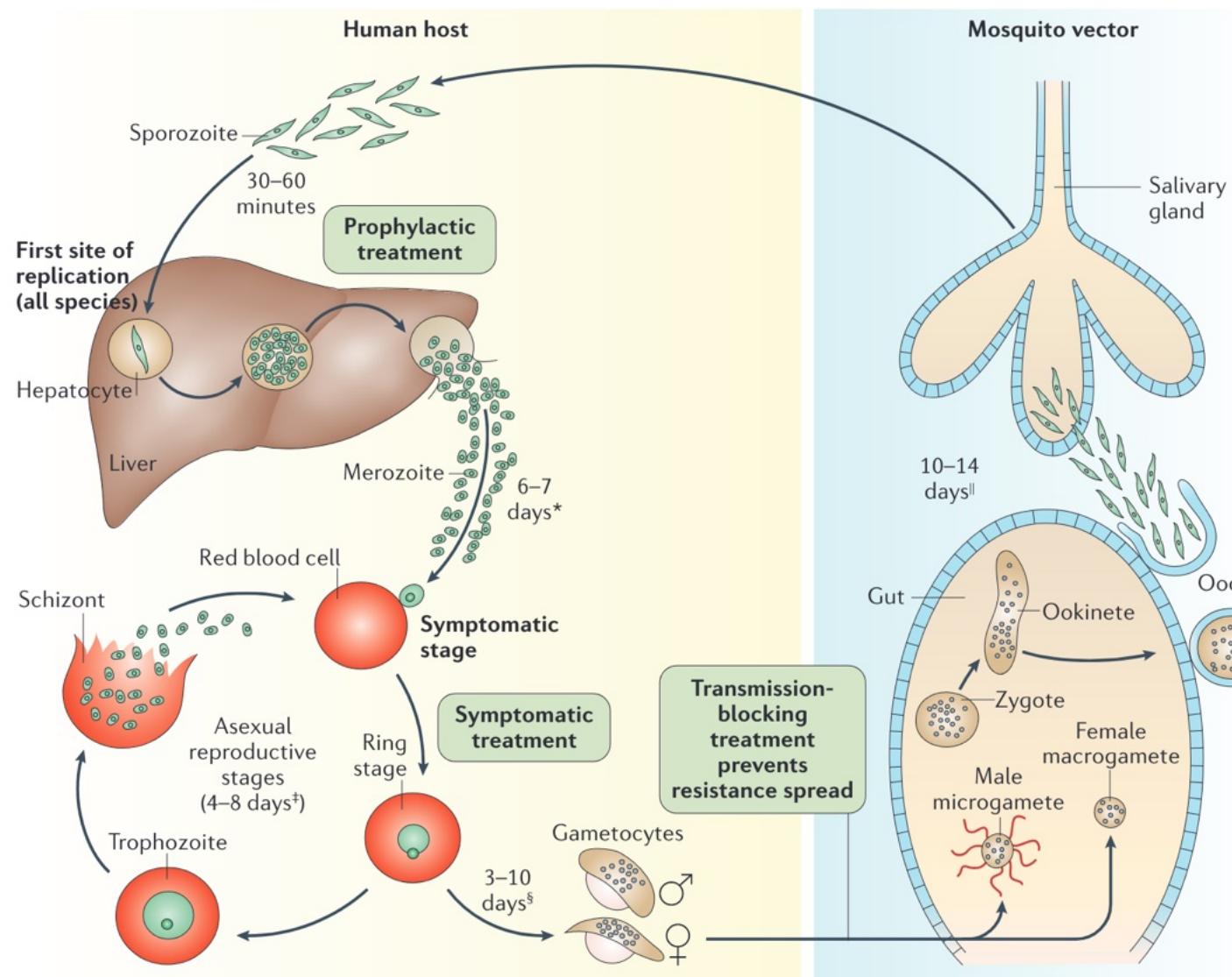
| The female Anopheles mosquito passes on the malaria parasite by feeding on human blood

"It's the first time in my 30-year career that I've seen a case of malaria originating in Trentino," said Dr Claudio Paternoster, an infectious diseases specialist at Trento's Santa Chiara Hospital. Since the 1950s, Italy has not had a malaria problem because mosquito-infested marshes were drained. There is speculation that Sofia might have caught malaria from one of two children treated for it at the Trento hospital after 15 August. They had caught it in Africa, and recovered.

Pathogenesis



Plasmodium spp. life cycle



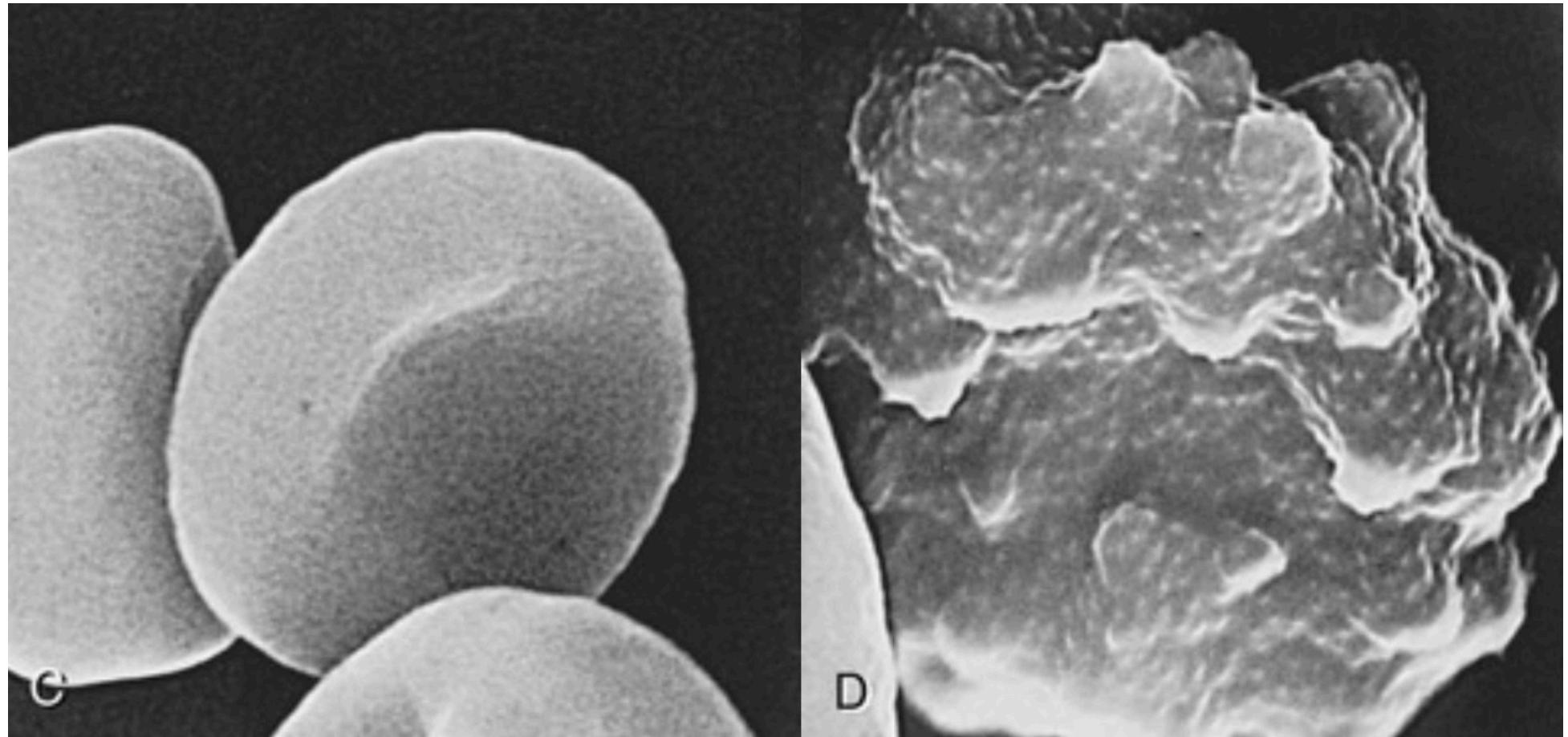
Clinical presentation

- First symptoms are typically experienced 2-4 weeks after mosquito bite
- Asexual replication in RBCs results in subsequent waves of merozoite and malaria endotoxin release (heamozoin and parasite DNA) → TNF- α and paroxysms of chills, fevers and sweats for several hours followed by extreme fatigue
- Cycle repeats every:
 - 24 hours *Plasmodium knowlesi*
 - 48 hours *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*
 - 72 hours *Plasmodium malariae*
- Some *P. vivax* and *P. ovale* can postpone development in liver as latent forms called hypnozoites (not eradicated by standard therapy e.g., chloroquine) directed against blood stages.
- Hypnozoite development can resume months to years later leading to relapse
 - Relapse can be prevented with primaquine, but only moderately effective

Five species of *Plasmodium* infection in humans

<i>Plasmodium</i> <i>spp.</i>	Liver stage	Blood cycle and fever peaks	Disease features
<i>P. falciprium</i>	6-14 days	48h (tertian)	Major complications, fatal without treatment
<i>P. vivax</i>	12- 17 days	48h (tertian)	Seldom fatal, but can better survive unfavourable temperatures and remain dormant in the liver
<i>P. malariae</i>	13- 40 days	72h (quartan)	Nephrotic syndrome
<i>P. ovale</i>	9-18 days	48h (tertian)	
<i>P. knowlesi</i>	9-12 days	24h (quotidian)	Southeast Asia, monkey

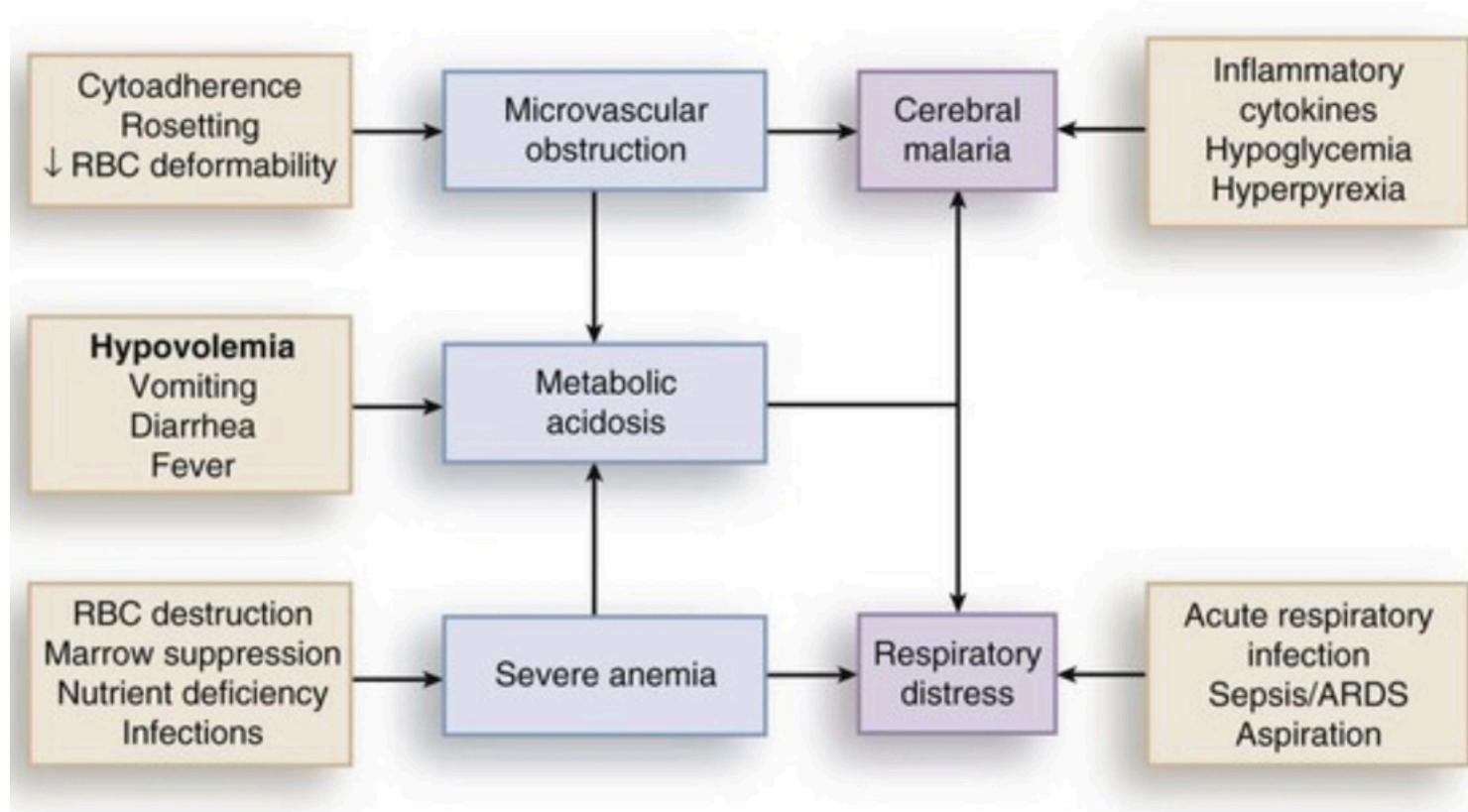
Plasmodium falciparum



SEM demonstrating effect of malaria parasite on host erythrocyte

Plasmodium falciparum

- Most deadly (1 million deaths per year- anaemia and cerebral malaria)
- Sequestration- parasitized RBCs: glomerulonephritis, hypoglycaemia, pulmonary edema
- Almost all deaths are caused by this species

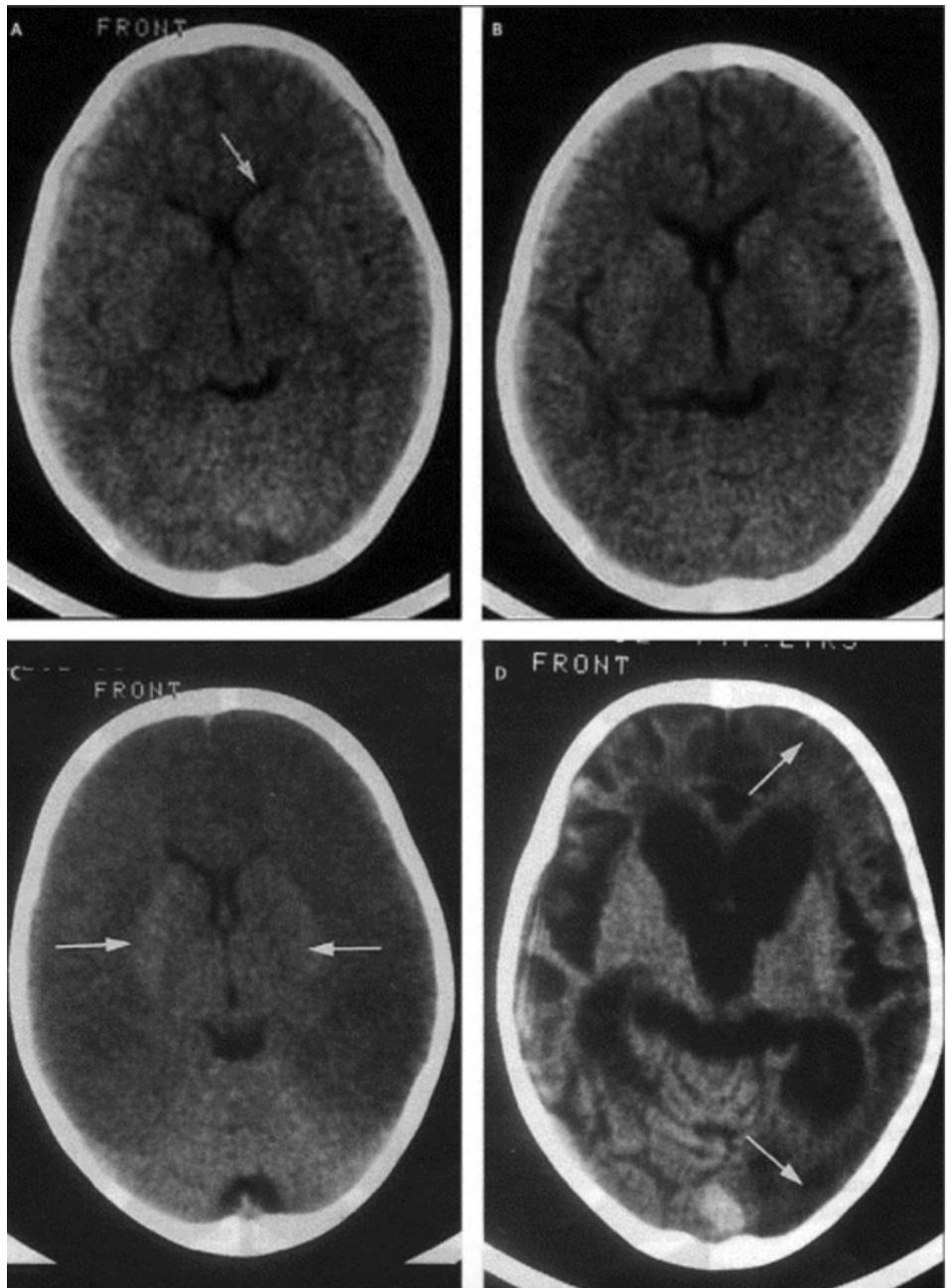


(Fairhurst, Rick and Wellem, Thomas, 2015)

Cerebral malaria

- Cerebral malaria (intense sequestration of infected erythrocytes in cerebral microvessels)
- Ring haemorrhages, perivascular leukocyte infiltrates, thrombin deposition
- Impairment of local delivery of oxygen and glucose
- Often does not produce neurological sequelae akin to thrombotic stroke
 - Recovery within 48 hours common

Imaging findings cerebral malaria

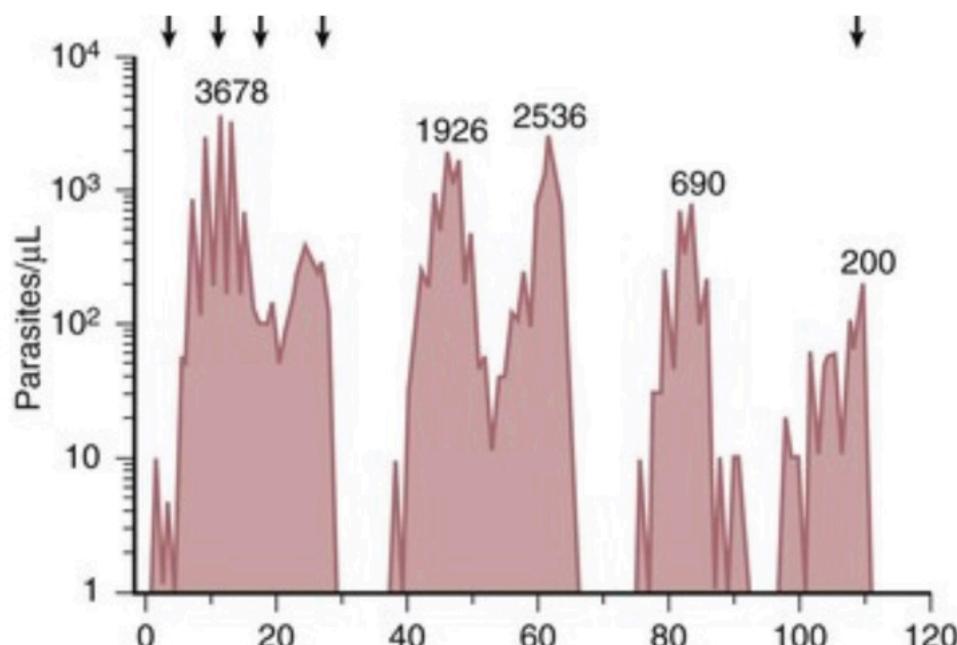


Increased brain volume and increased intracranial pressure

(Idro et al., 2005)

Malaria- acquired immunity

- Mediated by IgG antibodies against surface proteins of sporozoite (blocking hepatocyte invasion)
 - Antibody-dependent cellular cytotoxicity, opsonisation for uptake, destruction by splenic macrophages, interference with PfEMP-1 mediated cytoadherence interactions
- Immunity not sterilizing, instead “disease-controlling immunity” despite presence of parasites in bloodstream
- Immunity increases with age, cumulative episodes and time living in endemic area
 - Short-lived without continued exposure to different *P. falciparum* variants
 - Antigen switching results in new waves of parasitemia, escape from antibody responses
 - Disease controlling immunity (premunition) after repeated infection episodes associated with development of antibody repertoire that recognizes the full spectrum PfEMP-1 variant antigens



Host traits that influence disease severity (besides blood disorders)

- **Splenectomy** - high parasite loads
 - Splenomegaly common in malaria (removal of infected erythrocytes) but contributes to anaemia associated with disease
- **Pregnancy** - parasites that express protein surface variant antigen 2-CSA (chondroitin sulphate-2) attaching to glycoproteins expressed in the placenta ...leading to infected red blood cell sequestration in the placenta
 - Increased risk of maternal and/or foetal death, miscarriage, inter-uterine growth retardation, low-birth weight, increased newborn mortality
- **HIV** (higher degree of parasitemia, mortality)
- **Tuberculosis**

Complications of malaria

- Hypoglycaemia (coma, convulsions)

- Children: Impaired hepatic gluconeogenesis, increased glucose consumption in peripheral tissues and by parasites, **normal insulin levels**
- Adults: Hyperinsulinemia due to parasite stimulation of pancreatic islet cells or quinine/quinidine therapy
- Decreased food intake during prodromal period

- Anaemia

- Intra vascular lysis and phagocytic removal of infected erythrocytes
- TNF- α associated suppression of erythropoietin
- Normochromic, normocytic anaemia without robust reticulocyte response

- Pulmonary oedema and respiratory distress

- Non-cardiogenic pulmonary oedema due to sequestration of infected erythrocytes → inflammatory response → capillary permeability → pulmonary oedema → hypoxia → acute lung injury → ARDS
- Dyspnea and increasing respiratory rate are features of impending pulmonary oedema and preclude other clinical (e.g., accessory muscle breathing) and radiologic signs (increased interstitial markings)
- TNF- α associated suppression of erythropoietin
- Normochromic, normocytic anemia without robust reticulocyte response

- Pulmonary oedema and respiratory distress

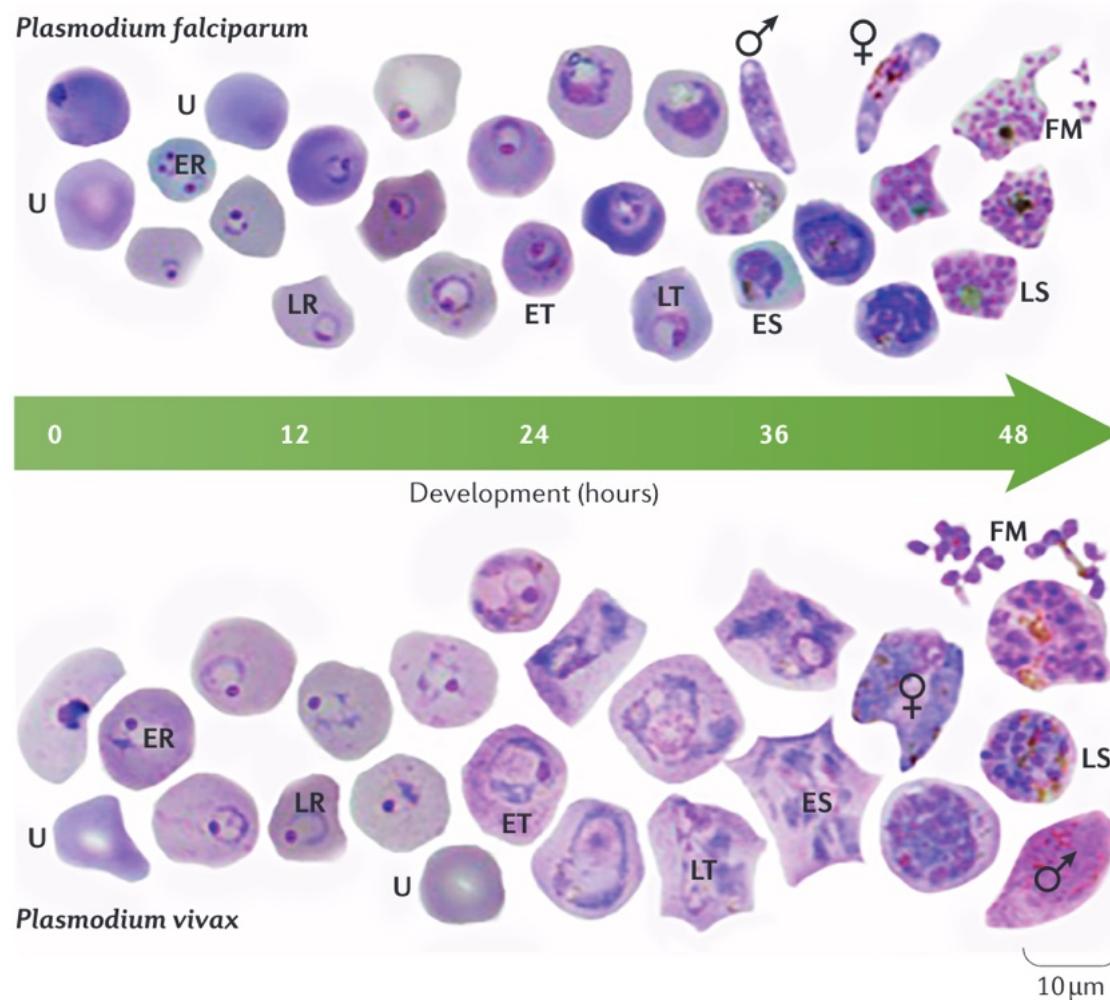
- Non-cardiogenic pulmonary oedema due to sequestration of infected erythromyctes →

Diagnosis and Screening

Clinical History

- **Febrile illness** (cyclic paroxysms of chills rigours and fever with drenching night sweats after travel to an endemic area)
 - Fever 100%
 - Headache 100%
 - Weakness 94%
 - Profuse night sweats 91%
 - Insomnia 61%
 - Arthralgias 59%
 - Myalgias 56%
 - Diarrhoea 13%
 - Abdominal cramps 8%
- **Physical exam**
 - Pallor
 - Hepatosplenomegaly
 - Jaundice, diminished consciousness, convulsions (severe malaria)
 - Less common (rash, lymphadenopathy, pulmonary consolidations)

Parasites can be detected on light microscope examination of blood smear

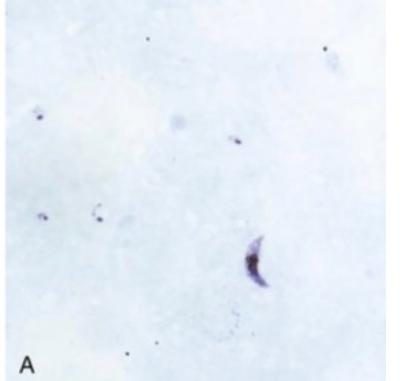
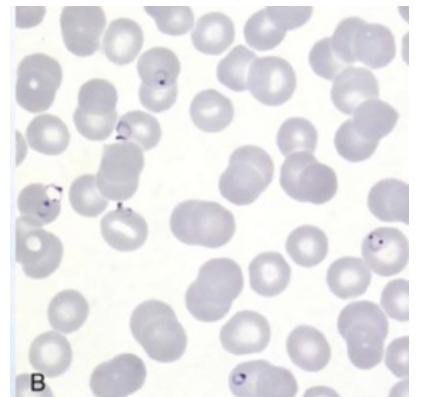


(Phillips et al., 2017) Microscopic images of parasite-infected red blood cells. Thin blood films showing Plasmodium falciparum (upper panel) and Plasmodium vivax (lower panel) at different stages of blood-stage development. The images are from methanol-fixed thin films that were stained for 30 minutes in 5% Giemsa. The samples were taken from Thai and Korean patients with malaria: Ethical Review

Parasitemia

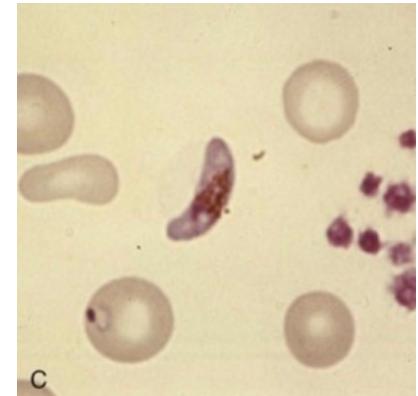
- Light microscopy of Giemsa-stained blood smears is the accepted standard for diagnosis
- Thick smears concentrate red cell layers 40-fold and used to screen large amounts of blood for parasites- RBCs lyse so parasites are visualized outside red cells
 - Parasite density can be calculated by counting the number of parasites per 200 WBCs x 40 = number of parasites per μL blood
 - For *P. falciparum*, initial blood smears may be negative because mature erythrocytes (trophozoites and schizonts are sequestered in peripheral tissues)
 - Smear is repeated every 12 hours until diagnosis is ruled in or ruled out
- Thin smears used to determine *Plasmodium* species

Microscopic images of parasite infected red blood cells

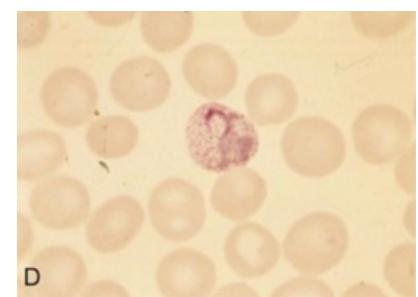
Description	Image
Multiple signet-ring <i>P. falciparum</i> trophozoites visualized outside erythrocytes in thick blood smear	 A
Multiply infected erythrocyte containing signet-ring <i>P. falciparum</i> trophozoites	 B

Description**Image**

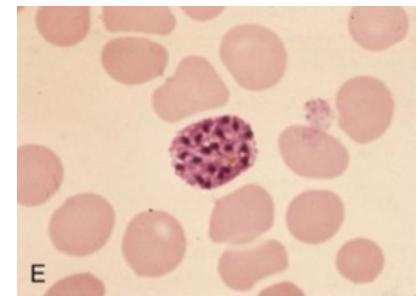
Banana-shaped gametocyte unique to *P. falciparum*



Ameboid trophozoite characteristic of *P. vivax*

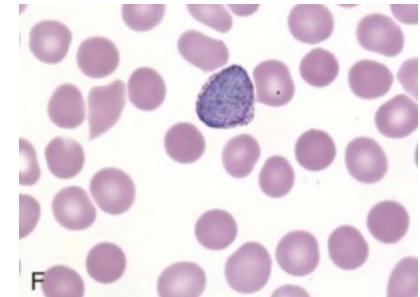


P. vivax schizont



Description**Image**

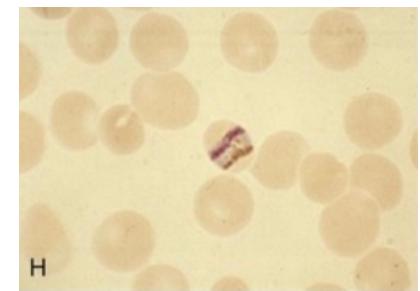
P. vivax spherical gametocyte



P. ovale trophozoite. Note Shuffner's dots and ovoid shape of erythrocyte



Characteristic band form trophozoite of *P. malariae* containing intracellular pigment hemozoin



Rapid diagnostic tests (RDTs)

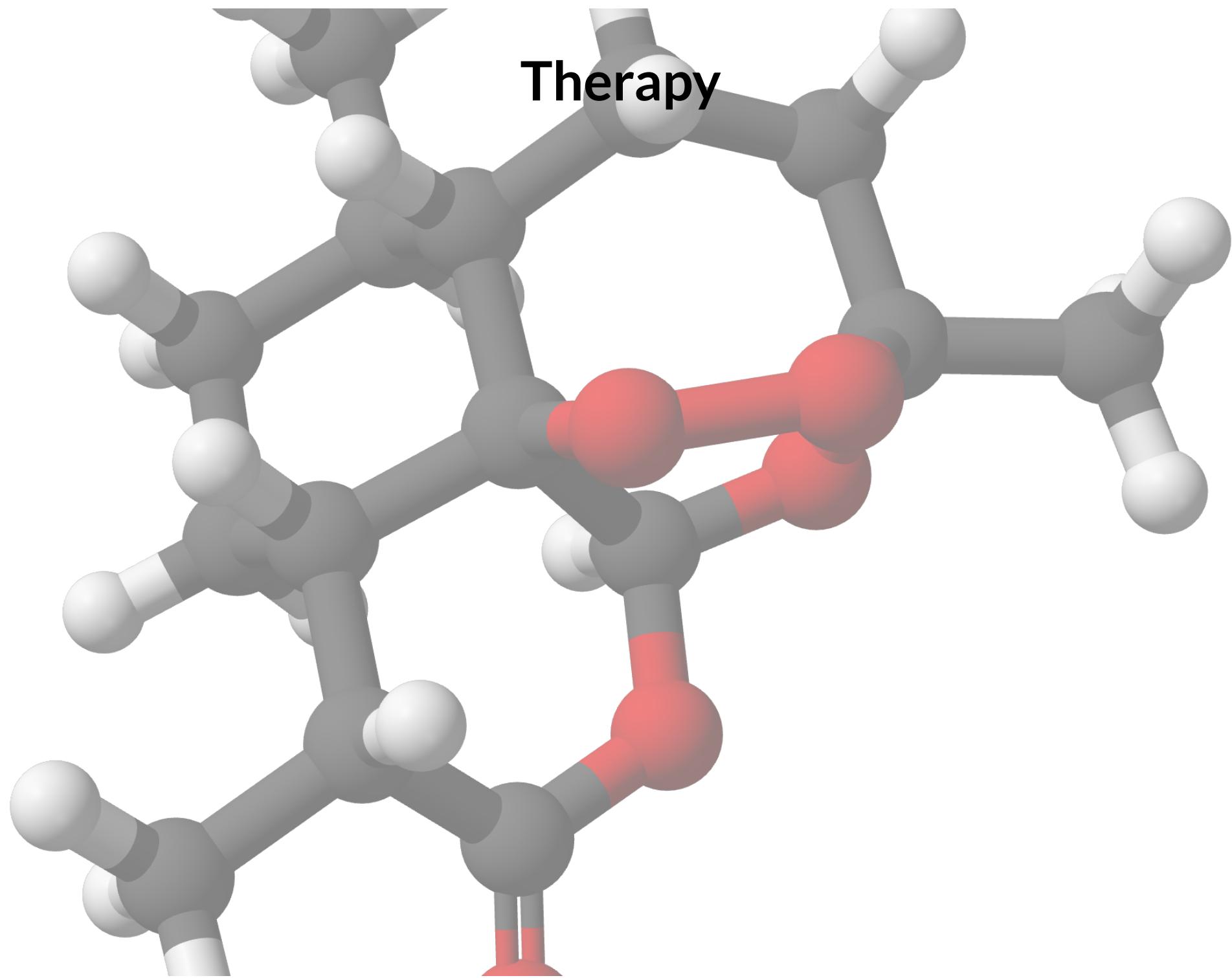
- Detection of *Plasmodium* histidine-rich protein-2 (HRP-2)
 - Limited to *P. falciparum*
 - Not useful for monitoring treatment response (positive for 28 days)
 - Less sensitive at parasite densities of 100-1000/ μL (may miss non-immune travellers with symptoms at low parasite densities)
- Detection of *P. falciparum* specific lactate dehydrogenase (LDH) and pan-*Plasmodium* LDH
 - Adequate sensitivity for *P. vivax*, *P. ovale*, and *P. malaria* with less sensitivity for *P. falciparum*
 - However, positive signal is proportional to *P. falciparum* parasitaemia, allowing for monitoring of therapeutic response
- Combination tests of HRP-2/LDH under development

Other laboratory tests

- Decreases in haemoglobin, hematocrit and haptoglobin and increases in LDH expected
- Leukocyte and platelet counts are

Diseases with similar clinical presentations

- Malaria should always fall near the top of the differential for fever in travellers or immigrants who have been in an endemic area in the previous 3 months (and remain in consideration for years afterward)
- Common differential diagnosis:
 - Influenzae
 - Enteric fever
 - Bacteremia/sepsis
 - Classic dengue fever (typically more severe myalgias , shorter incubation of 4-7 days, rash and lymphadenopathy)
 - Acute schistosomiasis (Katayama fever-freshwater exposure) urticaria at site of cercarial penetration (usually legs) and eosinophilia
 - Leptospirosis (conjunctival suffusion and rash progressing to haemorrhagic manifestations)
 - African tick fever (lymphadenitis, multiple inoculation eschars)
 - East African trypanosomiasis (sleeping sickness) -red chancre at bite site, posterior cervical lymphadenopathy, rash)
 - Yellow fever (conjunctival suffusion, shorter incubation period 3-6 days relative bradycardia). Unlikely in patients who have been vaccinated in last 10 years



Therapy

Definition of severe malaria

Manifestations	Definitions
Impaired consciousness	Glasgow coma score <11 in adults or Blantyre coma score <3 in children; inability to swallow
Prostration	Generalized weakness so that a person is unable to sit, stand, or walk without assistance
Multiple convulsions	More than two episodes within 24 hours
Acidosis	A base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Clinical indicators of acidosis include rapid, deep, labored breathing.
Hypoglycaemia	Blood or plasma glucose <40 mg/dL (<2.2 mmol/L) for children ≥5 years and adults; blood or plasma glucose <54 mg/dL (<3 mmol/L) for children <5 years
Severe anaemia	Haemoglobin concentration ≤5 g/dL or hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with parasite count >10,000 parasites/uL
Renal impairment	Plasma or serum creatinine >3 mg/dL (265 umol/L) or blood urea >20 mmol/L
Jaundice	Plasma or serum bilirubin >50 umol/L (3 mg/dL) with one of the following: - <i>Plasmodium falciparum</i> parasite count >2.5% parasitemia

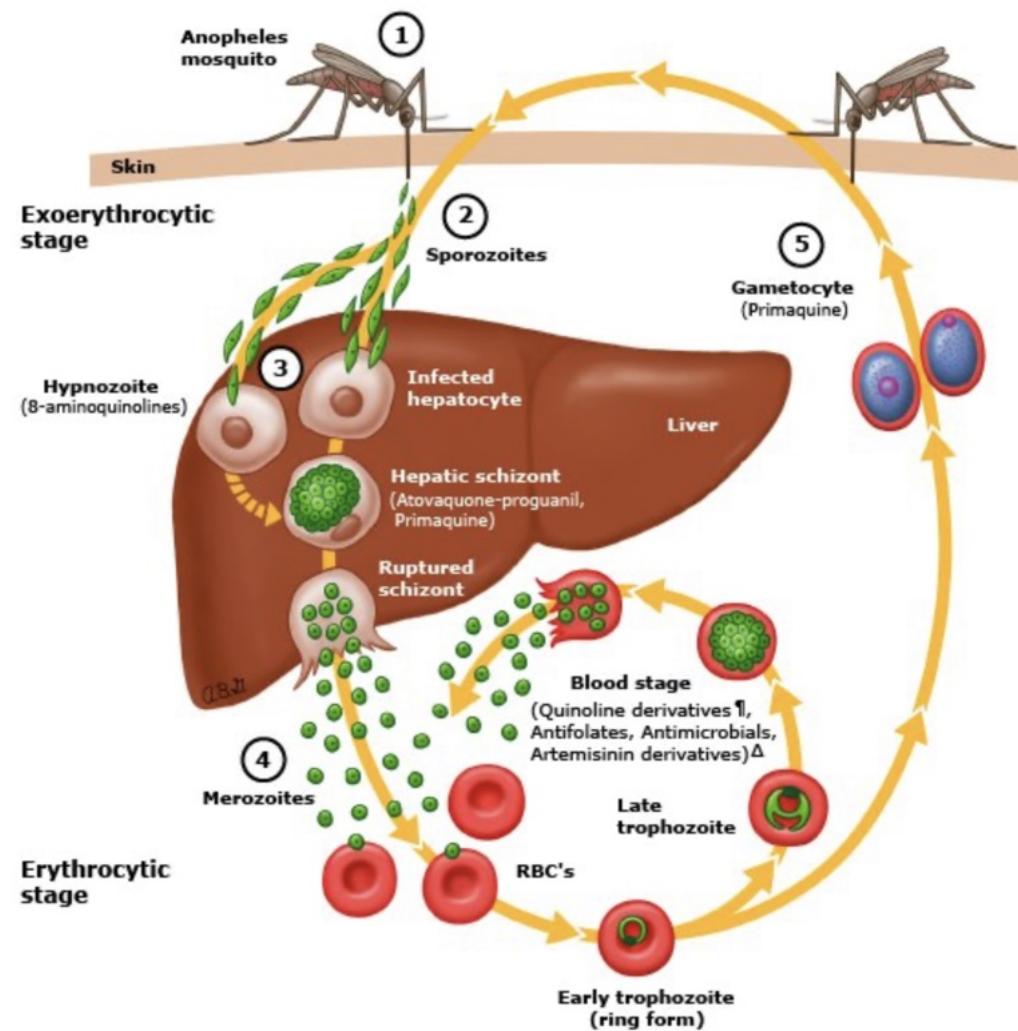
Manifestations	Definitions
	- <i>Plasmodium knowlesi</i> parasite count $>20,000$ parasites/uL
Pulmonary edema	Radiographically confirmed or oxygen saturation $<92\%$ on room air with respiratory rate >30 /minute, often with chest indrawing and crepitus on auscultation
Significant bleeding	Including recurrent or prolonged bleeding (from the nose, gums, or venipuncture sites), hematemesis, or melena
Shock	Compensated shock is defined as capillary refill ≥ 3 seconds or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mmHg in children or <80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
Hyperparasitaemia	<p><i>P. falciparum</i>:</p> <ul style="list-style-type: none"> - In non-immune travelers: parasitemia $\geq 5\%$[3] - All patients: parasitemia $>10\%$ <p><i>P. knowlesi</i>:</p> <ul style="list-style-type: none"> - Parasite density $>100,000$ parasites/uL <p><i>Plasmodium vivax</i>:</p> <ul style="list-style-type: none"> - No established parasite density thresholds

Therapy- General principles

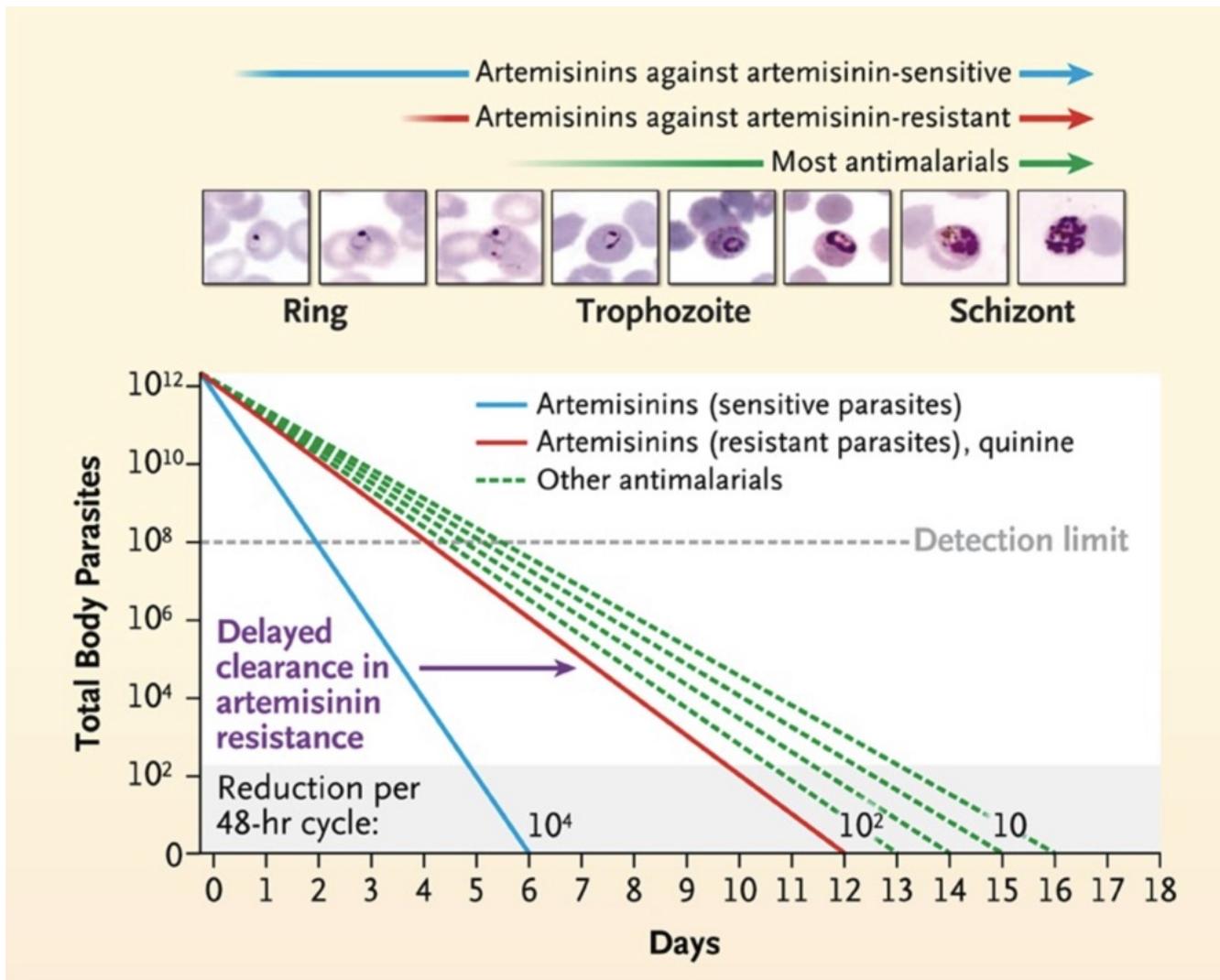
- *P. falciparum* malaria can be fatal if not diagnosed and treated promptly and appropriately
 - Especially true for non-immune travellers returning from visits to malaria-endemic areas
- Malaria is a disease of protean manifestations, diagnosis is delayed by non-specific clinical presentation and unimpressive normal laboratory tests- especially if blood smears (and available rapid diagnostic tests) are not examined
- Life-threatening manifestation (i.e. convulsions, hypoglycaemia, pulmonary oedema) can develop rapidly in patients who appear well at presentation or respond to antimalarial drugs
- Pregnant women, young children and elderly are at increased risk and should be hospitalized regardless
- If patient develops malaria despite prophylaxis, they should receive a different antimalarial regimen for treatment

Drug treatment versus parasitic life cycle

Life cycle of *Plasmodium**



Artemisinin parasite clearance



(Dondorp et al., 2011)

Artemisinin-based combination therapy (ACT)

- Low side effect profile
- Potent against all stages (asexual forms) of malaria
- Most rapid clearance time relative to other antimalarial drugs
- Administered in combination with second drug that has longer half life to forestall artemisinin resistance

WHO recommendations: Uncomplicated malaria treatment

Strong recommendation for , High certainty evidence

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following ACTs:

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine-pyrimethamine (SP)
- artesunate + pyronaridine (currently unGRADEd, anticipated to be updated in 2022)

Artesunate pyronaridine is included in the WHO list of prequalified medicines for malaria, the Model List of Essential Medicines and the Model List of Medicines for Children. The drug has also received a positive scientific opinion from the European Medicines Agency and undergone a positive review by the WHO Advisory Committee on Safety of Medicinal Products. Countries can consider including this medicine in their national treatment guidelines for the treatment of malaria based on WHO's position on the use of this drug pending the formal recommendation anticipated in 2021. WHO's position was published in the information note [The use of artesunate-pyronaridine for the treatment of uncomplicated malaria](#) (122) which clarifies that artesunate pyronaridine can be considered a safe and efficacious ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas.

In the absence of resistance to the partner drug, the five recommended ACTs have all been shown to achieve a PCR- adjusted treatment failure rate of 5% in many trials in several settings in both adults and children (high-quality evidence) See WHO guidelines for age and weight-specific dosing and toxicity risks in specific populations. Regimens should not be used for pregnant women in first trimester.

Duration of treatment

Treating uncomplicated *P. falciparum* malaria (2015)

Strong recommendation for , High certainty evidence

Duration of ACT treatment: ACT regimens should provide 3 days' treatment with an artemisinin derivative.

Evidence To Decision

Benefits and harms

Desirable effects

- Fewer patients taking ACTs containing 3 days of an artemisinin derivative experience treatment failure within the first 28 days (high-quality evidence).
- Fewer participants taking ACTs containing 3 days of an artemisinin derivative have gametocytaemia at day 7 (high-quality evidence).

(World Health Organization, 2022)

Treatment of pregnant patients

Strong recommendation for

Treat pregnant women with uncomplicated *P. falciparum* malaria during the first trimester with 7 days of quinine + clindamycin.

*unGRADEd recommendation, anticipated to be updated in 2022

(World Health Organization, 2022)

Relapse or Recurrence

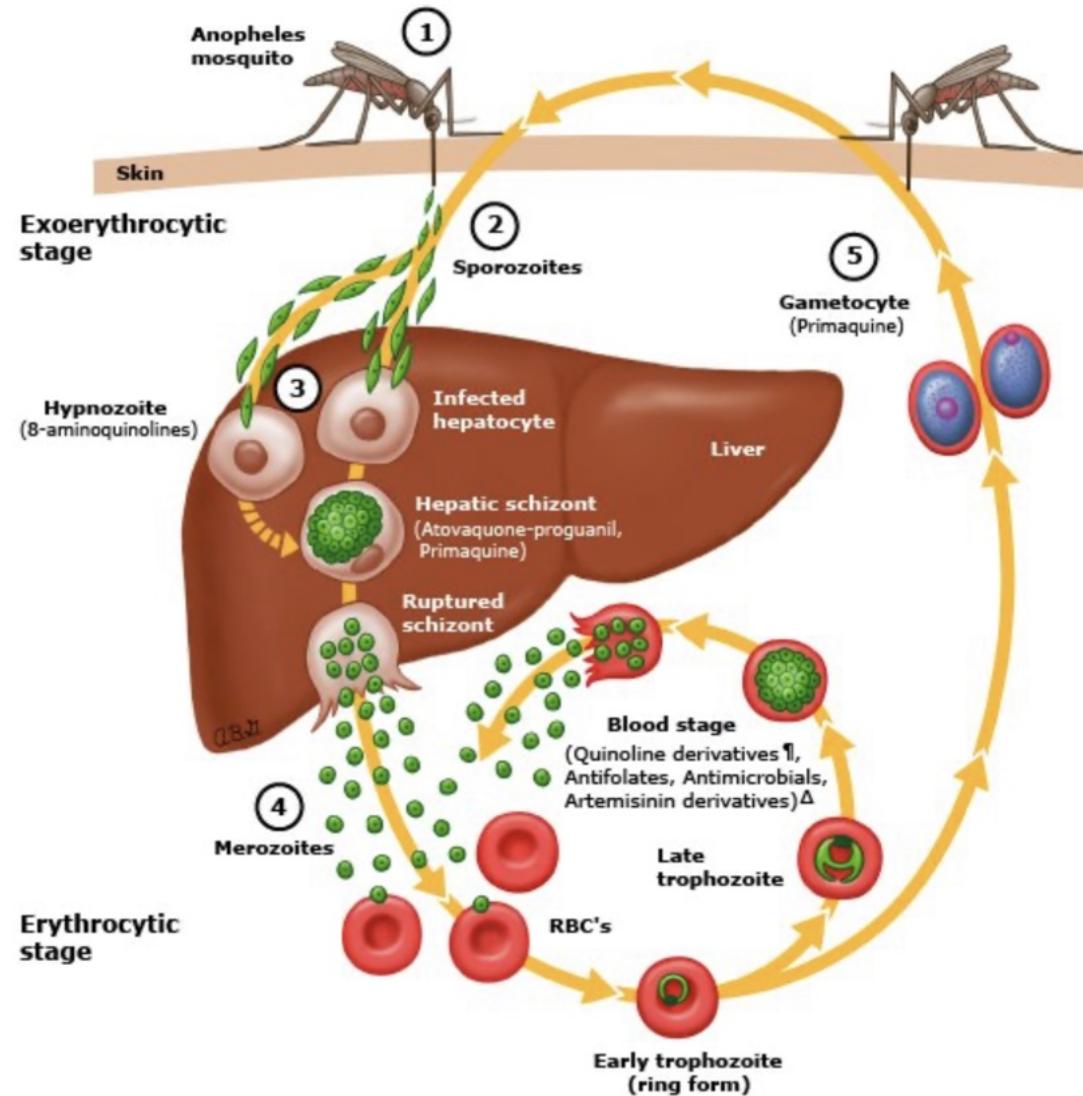
- Follow-up blood smears should document clearance of parasitemia within 48-72 hours of appropriate therapy. Follow-up smears every 12-24 hours are common.
- **Recurrence of *P. falciparum* malaria can result from re-infection or recrudescence (treatment failure)**
 - Failure :< 28 days: Persistent fever, parasitemia → treat with another ACT regimen effective in region. Treatment with same ACT considered if no second line regimens are available
 - Failure > 28 days: Likely re-infection: Treat with first-line ACT
- **Treatment failure may result from:**
 - Drug resistance
 - Inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual,
 - Substandard (counterfeited) medicine

Artemisinin resistance

- Southeast Asia, parts of sub-Saharan Africa, South America
- Consider in patients with epidemiological exposure
- Evaluation:
 - Malarial blood smear on day 3: Unlikely if parasite density < 3% with initial parasite density of > 100,000 parasites/ μL

Reducing transmissibility

Life cycle of *Plasmodium**



Reducing transmissibility

- Gametocytes may persist in blood after successful treatment of infection; not harmful to patient but serve as a source of ongoing transmission
- Single doses of primaquine > 0.4 mg/kg bw reduced gametocyte carriage at day 8 by around two thirds (moderate- quality evidence).

Strong recommendation for , Low certainty evidence

Reducing the transmissibility of treated *P. falciparum* infections: In low-transmission areas, give a single dose of 0.25 mg/kg bw primaquine with ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.

Avoid in pregnant patients and infants < 6 months

(World Health Organization, 2022)

Definition of severe malaria

Manifestations	Definitions
Impaired consciousness	Glasgow coma score <11 in adults or Blantyre coma score <3 in children; inability to swallow
Prostration	Generalized weakness so that a person is unable to sit, stand, or walk without assistance
Multiple convulsions	More than two episodes within 24 hours
Acidosis	A base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Clinical indicators of acidosis include rapid, deep, labored breathing.
Hypoglycaemia	Blood or plasma glucose <40 mg/dL (<2.2 mmol/L) for children ≥5 years and adults; blood or plasma glucose <54 mg/dL (<3 mmol/L) for children <5 years
Severe anaemia	Haemoglobin concentration ≤5 g/dL or hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with parasite count >10,000 parasites/uL
Renal impairment	Plasma or serum creatinine >3 mg/dL (265 umol/L) or blood urea >20 mmol/L
Jaundice	Plasma or serum bilirubin >50 umol/L (3 mg/dL) with one of the following: - <i>Plasmodium falciparum</i> parasite count >2.5% parasitemia - <i>Plasmodium knowlesi</i> parasite count >20,000 parasites/uL

Manifestations	Definitions
Pulmonary edema	Radiographically confirmed or oxygen saturation <92% on room air with respiratory rate >30/minute, often with chest indrawing and crepitus on auscultation
Significant bleeding	Including recurrent or prolonged bleeding (from the nose, gums, or venipuncture sites), hematemesis, or melena
Shock	Compensated shock is defined as capillary refill ≥3 seconds or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mmHg in children or <80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
Hyperparasitaemia	<p><i>P. falciparum</i>:</p> <ul style="list-style-type: none"> - In non-immune travelers: parasitemia ≥5%[3] - All patients: parasitemia >10% <p><i>P. knowlesi</i>:</p> <ul style="list-style-type: none"> - Parasite density >100,000 parasites/uL <p><i>Plasmodium vivax</i>:</p> <ul style="list-style-type: none"> - No established parasite density thresholds

Treatment of severe malaria

5.5.1 Artesunate

Strong recommendation for , High certainty evidence

Treat adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, complete treatment with 3 days of ACT.

Delayed haemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers.

When artesunate not available, artemether is considered as second line therapy followed by quinine (dihyrdochloride)- must be given by slow infusion or IM. ([World Health Organization, 2022](#))

Pre-referral treatment options

Strong recommendation for , Moderate certainty evidence

Where complete treatment of severe malaria is not possible, but injections are available, give adults and children a single intramuscular dose of artesunate, and refer to an appropriate facility for further care. Where intramuscular artesunate is not available use intramuscular artemether or, if that is not available, use intramuscular quinine.

Where intramuscular injection of artesunate is not available, treat children < 6 years with a single rectal dose (10mg/kg bw) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults.

(World Health Organization, 2022)

Prevention of malaria infection in travellers

- Areas chloroquine-resistant *P. falciparum*
 - Mosquito avoidance
 - Chemoprophylaxis (atovaquone-proguanil, mefloquine, doxycycline, tafenoquine)
 - Fewest side effects with atovaquone-proguanil
 - Weekly mefloquine
 - Doxycycline must be taken daily, sun sensitization
 - Test for G6PD deficiency before using tafenoquine
 - Start chemoprophylaxis prior to departure, continued regularly during travel, and continued for a time period after departure (duration is drug dependent)
 - Shortest discontinuation time is with atovaquone-proguanil and tafenoquine (one week)
- Other options are available for areas with chloroquine-sensitive *P. falciparum* or *P. vivax*

Vector control



A woman and child with bed nets in their home in Lupiro village, Tanzania.



Chemoprevention

- Seasonal malaria chemoprevention campaigns targeting children < 5 years
 - e.g., monthly treatment with sulfadoxine-pyrimethamine treatment during rainy season, > 80% reduction in malaria cases, with > 50% reduction in mortality
 - Rebound effect? Child loses immunity, treatment stopped because of age limit, social instability, resistance

Vaccine prospects

WHO recommends groundbreaking malaria vaccine for children at risk

Historic RTS,S/AS01 recommendation can reinvigorate the fight against malaria

6 October 2021 | News release | Geneva | Reading time: 3 min (859 words)



Leishmania infections

Tissue smear from patient with *Leishmania*

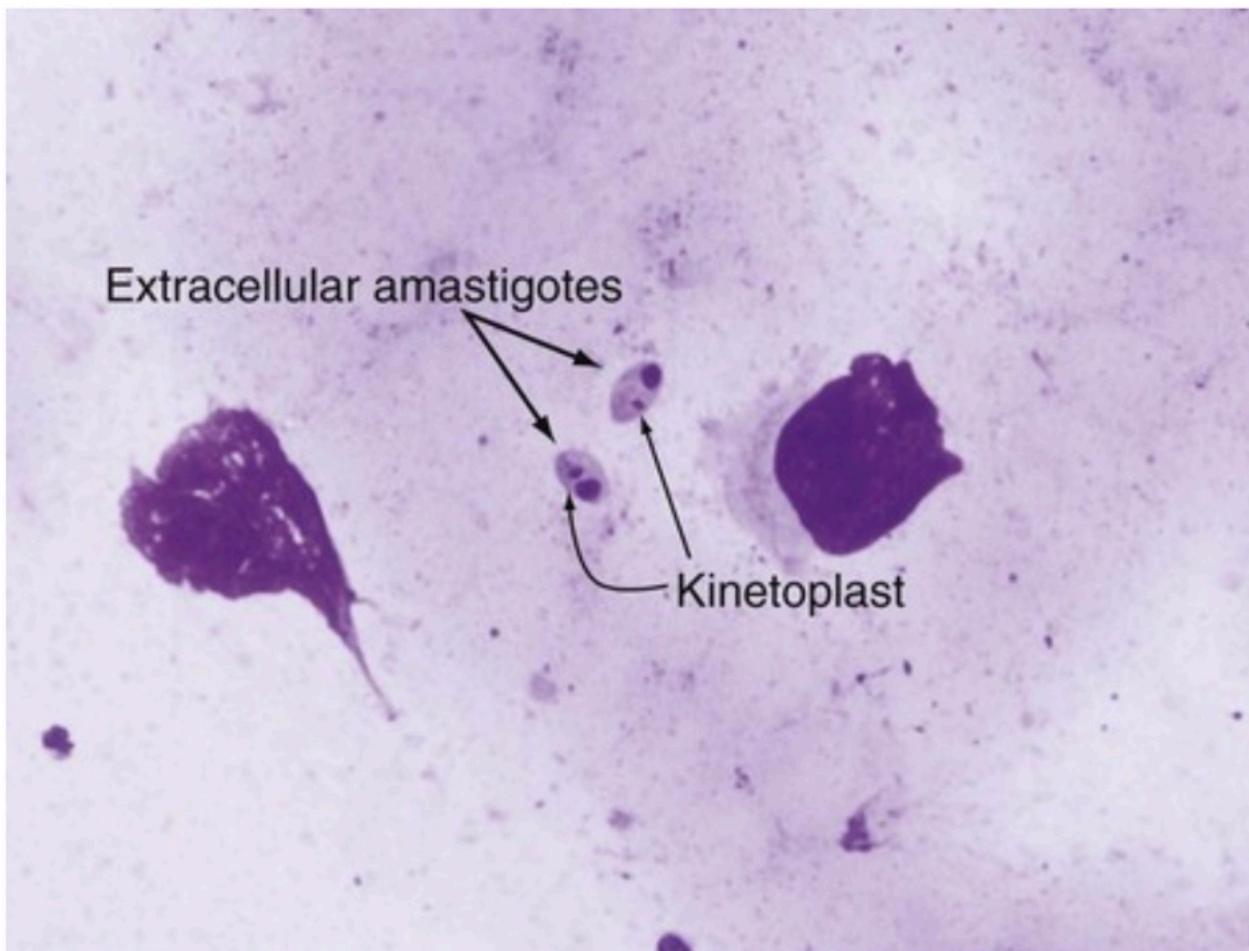


FIGURE 277-1 Tissue smear obtained from a patient with confirmed *Leishmania major* infection. Amastigotes, 3 to 4 μm in width and 4 to 5 μm in length are seen. Note the rod-shaped kinetoplast seen next to the nucleus. (Giemsa stain, magnification $\times 1000$). (Courtesy Dr. Peter Weina, Bethesda, MD.)

Leishmaniasis classification

CLINICAL SYNDROMES	LEISHMANIA SPP.	LOCATION
Visceral leishmaniasis (VL) (also known as kala-azar): generalized involvement of the reticuloendothelial system (spleen, bone marrow, liver, lymph nodes)	<i>Leishmania donovani</i> causes classic VL in Asia	Major endemic/epidemic focus in Indian subcontinent (lowland Terai region of southern Nepal, Bangladesh, Bihar province, and surrounding areas in India) Endemic/sporadic in China, Pakistan, Indian subcontinent
	→ <i>Leishmania infantum</i> causes infantile VL in the Old World. <i>Leishmania chagasi</i> / <i>L. infantum</i> causes VL in the Americas	Middle East, Mediterranean littoral, Balkans, Central and southwestern Asia, northern and western China, North and sub-Saharan Africa, Latin America
	<i>Leishmania donovani</i> / <i>L. infantum</i>	East Africa: Ethiopia, Kenya, Somalia, Sudan, Uganda
	<i>Leishmania amazonensis</i> is uncommon cause of atypical VL in the Americas	Brazil (Bahia state)
	<i>Leishmania tropica</i> is rarely associated with VL syndrome, often atypical	Middle East, Saudi Arabia (U.S. troops), India, North Africa, Pakistan, Mediterranean littoral, Central and western Asia
Post-kala-azar dermal leishmaniasis	<i>L. donovani</i> <i>L. donovani</i> / <i>L. infantum</i>	Indian subcontinent East Africa: Ethiopia, Kenya, Somalia, Sudan, Uganda
Old World cutaneous leishmaniasis: single or limited number of skin lesions	<i>Leishmania major</i> (also known as moist or rural oriental sore) <i>Leishmania tropica</i> (also known as dry or urban oriental sore) <i>Leishmania aethiopica</i> <i>L. infantum</i> / <i>L. chagasi</i> (rare) <i>L. donovani</i> / <i>L. infantum</i>	Middle East, India, Pakistan, Africa, Central and western Asia, northern and western China Mediterranean littoral, Middle East, North Africa, India, Pakistan, Central and western Asia Ethiopian highlands, Kenya, Yemen Middle East, Mediterranean littoral, Central Asia, northern and western China, North and sub-Saharan Africa East Africa: Ethiopia, Kenya, Somalia, Sudan, Uganda
New World cutaneous leishmaniasis: single or limited number of skin lesions	<i>Leishmania mexicana</i> (chiclero's ulcer) <i>L. amazonensis</i> <i>Leishmania pifanoi</i> <i>Leishmania garnhami</i> <i>Leishmania venezuelensis</i> <i>Leishmania (Viannia) braziliensis</i> <i>Leishmania (V.) guyanensis</i> (forest yaws or pian bois) <i>Leishmania (V.) peruviana</i> (uta) <i>Leishmania (V.) panamensis</i> <i>Leishmania (V.) colombiensis</i> <i>L. infantum</i> / <i>L. chagasi</i>	Central and South America, Texas Amazon Basin, neighboring areas, Bahia and other states of Brazil Venezuela Venezuela Venezuela Central and South America Guyana, Surinam, northern Amazon Basin Peru (western Andes) Panama, Costa Rica, Colombia Colombia and Panama Central and South America
Leishmaniasis recidivans	<i>L. tropica</i>	North Africa, Afghanistan, and Middle East
Diffuse cutaneous leishmaniasis	<i>L. amazonensis</i>	Amazon Basin, neighboring areas, Bahia and other states of Brazil
	<i>L. pifanoi</i>	Venezuela
	<i>L. mexicana</i>	Central and South America, Texas
	<i>Leishmania</i> spp.	Dominican Republic
	<i>L. aethiopica</i>	Ethiopian highlands, Kenya, Yemen
Disseminated leishmaniasis	<i>L. (V.) braziliensis</i>	Brazil
	<i>L. (V.) amazonensis</i>	
American mucosal leishmaniasis	<i>L. (V.) braziliensis</i> (espundia)	Central and South America; most cases from Bolivia, Brazil, and Peru
	Other <i>Leishmania</i> (V.) spp. (<i>guyanensis</i> , <i>panamensis</i>) are rare	Central and South America

Distribution of cutaneous leishmaniasis

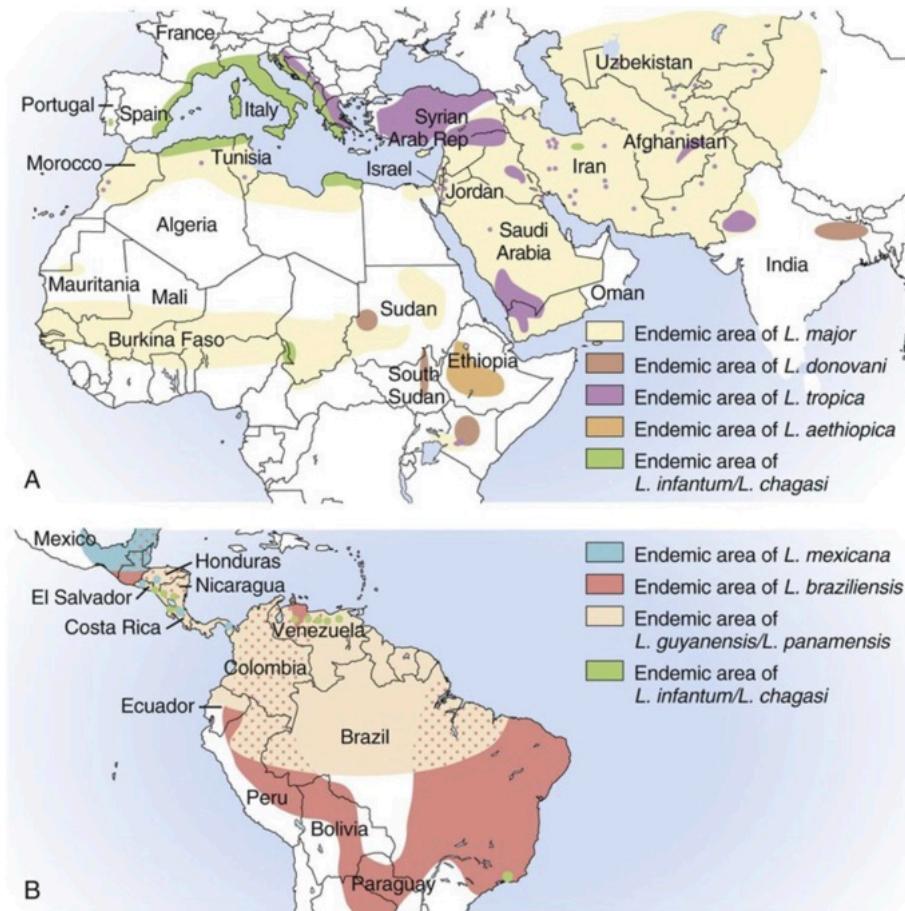


FIGURE 277-2 Distribution of cutaneous leishmaniasis (CL). **A**, Old World (Eastern Hemisphere) CL. **B**, New World (Western Hemisphere) CL. Other species causing CL in the New World are not shown but can be found in [Table 277-1](#).

Distribution of visceral leishmaniasis

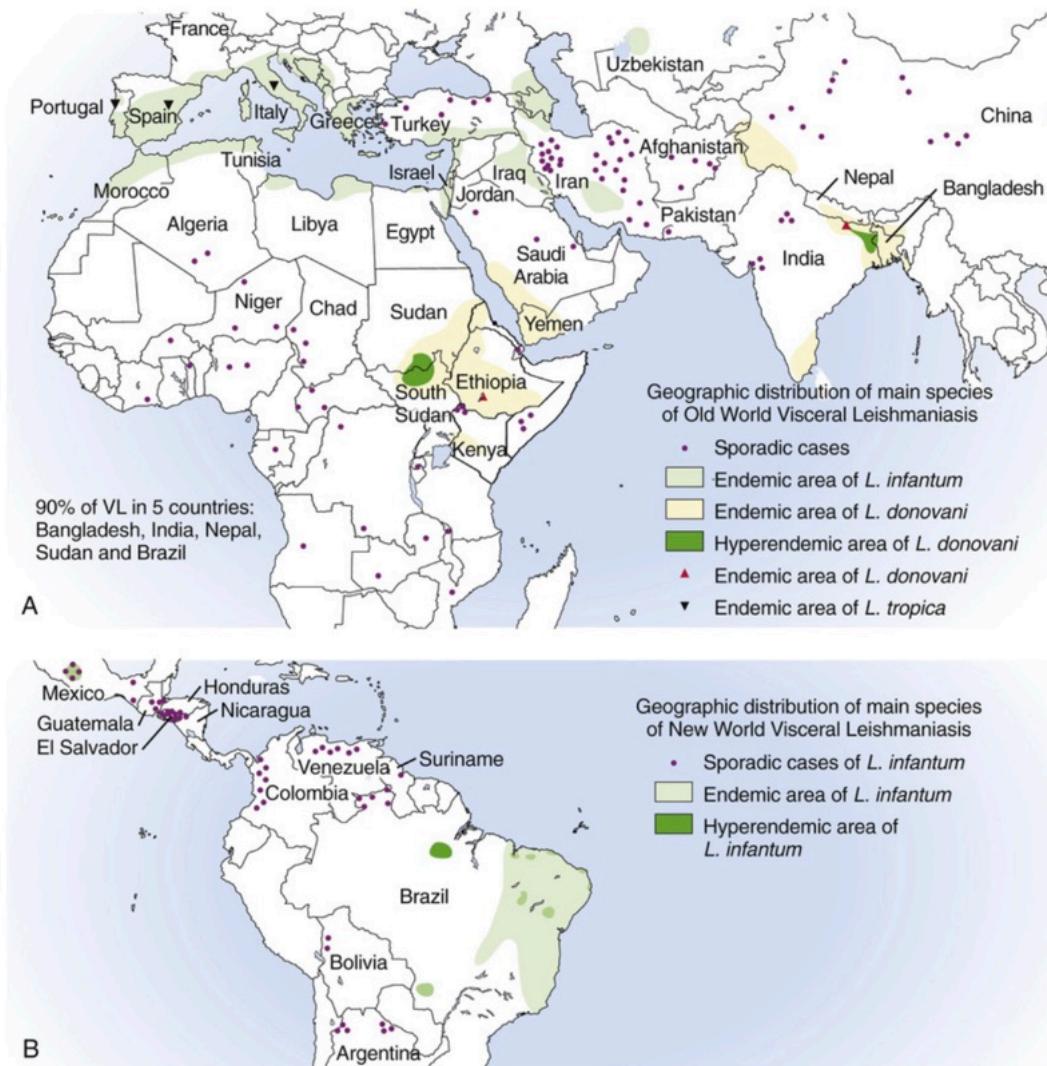
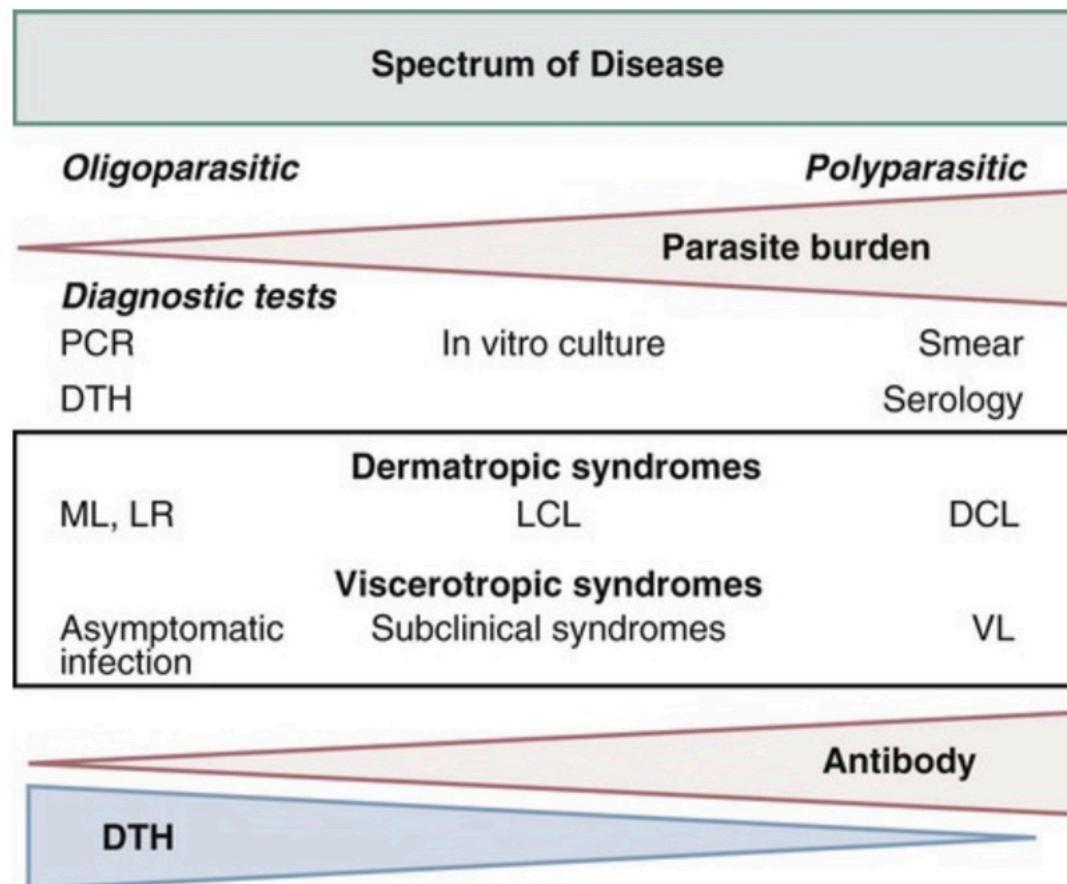


FIGURE 277-3 Distribution of visceral leishmaniasis (VL). **A**, Old World (Eastern Hemisphere) VL. **B**, New World (Western Hemisphere) VL.

Spectrum of Leishmania infection and disease



Hyperergic **Anergic**

FIGURE 277-5 Spectrum of *Leishmania* infection and disease. DCL, diffuse cutaneous leishmaniasis; DTH, delayed-type hypersensitivity; LCL, localized cutaneous leishmaniasis; LR, leishmaniasis recidivans; ML, mucosal leishmaniasis; PCR, polymerase chain reaction; VL, visceral leishmaniasis.

Pathophysiology

- *Leishmania* invade and replicate inside host macrophages
- Many infections are asymptomatic (subclinical), reflecting the host ability to control the infection
- Subclinical infections can reactivate during periods of immunosuppression

Classic presentation of VL (kala-azar)

- Prolonged fever
- Weight loss
- Hepato- splenomegaly
 - Parasite replicate in reticuloendothelial system (RES), with high parasite loads accumulating in liver, spleen and bone marrow
- Pancytopenia (due to bone marrow suppression)
- Hypergammaglobinumeia (polyclonal B cell activation)
- Late in course of infection thrombocytopenia and liver dysfunction
- Uniformly lethal without treatment

Clinical manifestations

- incubation period (2-8 months) but can be as short as 8-10 days
- Clinical disease may first become symptomatic years after exposure in patients who are immunocompromised
- Insidious development: fever, weakness, loss of appetite, weightloss, failure to thrive, abdominal enlargement caused by hepatosplenomegaly
- Acute presentation in non-immune patients with high fever and chills, sometimes with a periodicity suggestive of malaria
 - Spleen can become massively enlarged, soft and non-tender -Elevated liver enzymes and bilirubin occasionally present
- Patients often become cachetic with petechia and ecchymoses with possible epistaxis and gingival bleeding

Protruding abdomen with hepatosplenomegaly



FIGURE 277-6 Children with visceral leishmaniasis in Kenya. Note signs of malnutrition and protruding abdomen with massive hepatomegaly. (Courtesy Dr. Charles Oster, Washington, DC.)

Diagnosis Pentad

- Prolonged fever
- Progressive weight-loss
- Pronounced splenomegaly
- Pancytopenia
- Hypergammaglobulinemia



Diagnosis confirmation

- Parasitologic diagnosis: Amastigotes in tissues
- Isolation of promastigotes in cultures
- Splenic aspiration, liver biopsy, lymph node or bone marrow aspirates (safer but lower sensitivity)
- PCR assay
- Antileishmanial antibodies

Treatment

- Liposomal amphotericin B 10 mg/kg two consecutive days or 3 mg/kg days 1-5, 14, and 21
- Amphotericin B deoxycholate 1 mg/kg for 15 days or 1 mg/kg every other day for 30 days
- Pentamidine (hypotension, hypoglycemia, insulin-dependent diabetes mellitus)
- Miltefosine (oral, GI toxicity, elevated liver transaminases)

Treatment response

- Fever resolution (1-2 weeks)
- Decrease in spleen size over 1 month
- Weight gain
- Patients need to be followed for 12 month and instructed to return if symptoms recur.

References

- Dondorp AM, Fairhurst RM, Slutsker L, MacArthur JR, M. D. JGB, Guerin PJ, et al. The Threat of Artemisinin-Resistant Malaria. *New England Journal of Medicine* 2011;365:1073–5. <https://doi.org/10.1056/nejmp1108322>.
- Fairhurst, Rick, Wellems, Thomas. Malaria (plasmodium species). 8th ed., Elsivier; 2015.
- Idro R, Jenkins NE, Newton CR. Pathogenesis, clinical features, and neurological outcome of cerebral malaria. *The Lancet Neurology* 2005;4:827–40. [https://doi.org/10.1016/S1474-4422\(05\)70247-7](https://doi.org/10.1016/S1474-4422(05)70247-7).
- Kwiatkowski DP. How malaria has affected the human genome and what human genetics can teach us about malaria. *American Journal of Human Genetics* 2005;77:171–92.
- Phillips MA, Burrows JN, Manyando C, Huijsdijnen RH van, Van Voorhis WC, Wells TNC. Malaria. *Nature Reviews Disease Primers* 2017;3:17050. <https://doi.org/10.1038/nrdp.2017.50>.
- Tatem AJ, Rogers DJ, Hay SI. Estimating the malaria risk of african mosquito movement by air travel. *Malaria Journal* 2006;5:57. <https://doi.org/10.1186/1475-2875-5-57>.
- World Health Organization. WHO guidelines for malaria 2022.

