INMED HUMANITARIAN HEALTH CONFERENCE

TROPICAL DISEASES OF SIGNIFICANCE

MALARIA – DAUNTING CHALLENGES WITH HOPEFUL HORIZONS

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SESSION OBJECTIVES

- Understand the Epidemiology and some Pathophysiology
- Know the criteria for Diagnosing this widespread tropical disease
- Understand the Triage Criteria for disease severity
- Implement Treatment Options effectively
- Know the proper Preventive Measures available for yourself and the local population

DISCLOSURE

- There are no relevant financial relationships with ineligible companies to disclose.

OVERVIEW

- Malaria is the most important parasitic disease of humans
  - It is endemic throughout most of the tropics
- Since 2020, there has been an increase in cases and deaths due to the interruption of services attributable to the COVID-19 Pandemic
- The emergence of partial drug resistance to the primary treatment medication in the African region by the deadliest species, *Plasmodium falciparum,* is of great concern
- Mutations of *Plasmodia* rendering RDTs (Rapid Diagnostic Tests) ineffective must be kept in mind
- Furthermore, increasing reports of *Anopheles* mosquito resistance to pyrethroid insecticides poses more challenges

EPIDEMIOLOGY / WORLDWIDE DISEASE BURDEN

- According to the WHO's (World Health Organization) World Malaria Report 2025:
  - Almost half of the world's population – throughout most tropical regions including 80 countries and territories – live in areas at risk of Malaria
  - Marked increase in Malaria cases and deaths reported in 2024
    - ~282,000,000 cases of Malaria occurred worldwide (~19 Million increase from 2023)
      - Causing ~610,000+ deaths (including ~440,000 African Children <5y)
    - All told: the WHO Africa Region accounts for 95% of the global burden of malarial cases and deaths
      - Where it is also the single leading infectious cause of disability and death for <5y
      - The other high-risk group is pregnant women who may suffer profound anemia and deliver low birthweight newborns
- Regarding Malaria in the U.S.: In 2023, the first locally acquired (autochthonous) mosquito-transmitted Malaria cases in 20 years occurred with 10 cases (mostly *P. vivax*) identified in 4 states
  - While the risk of locally acquired Malaria in the U.S. remains very low, the 2023 outbreak proves that local transmission is possible

[SEE: PAGE 14 – GLOBAL MALARIA MAP]

6 SPECIES OF THE PROTOZOAN PARASITE *PLASMODIUM*

- ***P. FALCIPARUM***
  - *P. falciparum* is most prevalent worldwide & causes the most serious disease
    - Often simply referred to as "Falciparum Malaria"
  - Predominates throughout Africa, Hispaniola (Haiti and the Dominican Republic), and New Guinea
  - Multiplies rapidly in the blood potentially causing Severe Anemia
  - May clog small blood vessels in the brain resulting in potentially fatal "Cerebral Malaria" [see below]
    - An encephalopathy that presents with impaired consciousness, delirium, and/or seizures
- ***P. VIVAX* AND *P. OVALE***
  - ***P. vivax*** ranks second in global disease burden and is more common in Africa, Asia, the South Pacific, and Central and South America
    - ~80% of the global *P. vivax* burden arises from 4 countries: India, Pakistan, Ethiopia, and Sudan
    - Among travelers returning to North America or Europe, those visiting India/Pakistan are at greatest risk
  - ***P. ovale*** is especially recognized in tropical West Africa (but is also endemic in Southeast Asia and Oceania)
  - In Adults, only occasionally do these two species cause severe/life-threatening disease
    - With Severe ***P. vivax***, mortality ranges from 5–25%
      - Patients may manifest pulmonary complications and ARDS (Adult Respiratory Distress Syndrome)
    - With Severe ***P. ovale***, mortality estimates are 0.15%
  - However, in Children, both ***P. vivax*** and ***P. ovale*** can cause serious illness
  - ***P. vivax*** and ***P. ovale*** from topical strains also cause most late relapses (>80% and ~10% respectively)
    - Relapses can activate weeks, months, or even 2–3 years after the initial infection
      - Due to persistent liver stage parasites (hypnozoites)
- ***P. MALARIAE***
  - Relatively uncommon outside of sub-Saharan Africa and Southeast Asia (also, Oceania and South America)
  - Generally milder clinical disease in most Adults
    - Although severe complications do occur infrequently in Adults
      - Mortality is estimated at ≤2.4%
  - Characterized by years of low-grade asymptomatic parasitemia
    - Unique ability to cause attacks even decades after exposure
  - May (exclusively) cause Nephrotic Syndrome of the kidneys in Children
    - Occurs in ~5% of Children <5y infected with *P. malariae*
    - Unless treated early and aggressively, most of these Children die in <2 years
- ***P. KNOWLESI***
  - Originally a Malaria species of primate animals – natural hosts are Macaques
  - Human disease first described in 2004
  - Not yet proven to be transmitted from humans to mosquitoes, i.e., a monkey reservoir may be required
  - Occurs throughout Southeast Asia
  - Most patients have uncomplicated disease
    - Nevertheless, Adults with suspected *P. knowlesi* require hospitalization for management
  - Severe disease may occur in Adults, but has not been observed in Children
    - Clinical clues: Very ill patient, Malaria species looks like *P. malariae* on smear
- ***P. SIMIUM***
  - A Malaria species resembling *P. vivax*
  - Occurs in primates, but also has been found in humans in Brazil

MOSQUITOES: THE BANE OF HUMAN EXISTENCE

- An opinion article in the *NYTimes* by Timothy Winegard in 2019 made this unsettling statement:
  - Mosquitoes have, in general, remained the "Apex Predator / Killer" of humans throughout history!
  - Estimating that 52 BILLION humans have been killed by mosquito-borne diseases

THE VECTOR – *ANOPHELES* MOSQUITOES

- Globally: ~3,500 species of mosquitoes
  - Including ~430 *Anopheles* species
    - Only 60–70 can transmit Malaria, with ~40 of major importance (i.e., as "vectors") in nature
- Human Malaria is transmitted only by females of the genus *Anopheles*
  - Female *Anopheles* mosquitoes bite from "dusk to dawn", i.e., twilight hours and throughout the night
    - A blood meal is necessary for the female mosquito to produce her eggs
  - Unlike the human host, the mosquito vector does not suffer from the parasites
  - Long lifespan and strong human-biting habits of the African *Anopheles* mosquito vector species are among the primary reasons why ~95% of the world's Malaria cases are in Africa

OTHER MODES OF TRANSMISSION

- Other comparatively rare mechanisms for transmission include:
  - Congenitally acquired disease
  - Blood transfusion
  - Sharing of contaminated needles
  - Nosocomial transmission

LIFE CYCLE OF THE PLASMODIUM PARASITE

[SEE: PAGES 15-16 – DIAGRAM AND LEGEND]

- In Humans: After being bitten by a Sporozoite-infected mosquito, parasites grow and multiply first in liver cells → Red blood cells (RBCs)
- In the blood, successive broods of parasites grow inside the RBCs and destroy them, releasing daughter parasites ("merozoites") that continue the cycle by invading other RBCs
  - Release of merozoites from infected RBCs when they rupture triggers the fever and other clinical manifestations of Malaria
- Certain forms of blood stage parasites ("gametocytes") are picked up by another biting female *Anopheles* mosquito → a different cycle of growth and multiplication inside of the mosquito
- After 10–18 days, (i.e., the "external incubation period"), the parasites (as "sporozoites") populate the mosquito's salivary glands
  - Note: if a mosquito does not survive longer than the extrinsic incubation period, then she will not be able to transmit any Malaria parasites
- After the *Anopheles* mosquito bites another human, infection occurs when these sporozoites parasitize the liver

POPULATIONS AT GREATER RISK

- Certain populations are at considerably higher risk of contracting Malaria and developing SEVERE disease:
  - Children ages 6m – 59m
  - Pregnant women, esp. in the 2nd and 3rd trimesters
    - With Severe disease: Maternal mortality / adverse fetal outcomes ~50%
  - Patients with HIV/AIDS or other immunocompromised condition
  - Non-immune migrants
  - Mobile populations and Travelers

IMMUNITY

- Complete immunity does not occur
  - Rather are considered either "semi-immune" or "non-immune"
- Semi-immunity is partial immunity developed over years of exposure in high-transmission areas
  - Thereby, "reducing the risk" of Severe disease
  - Thus, most Malaria deaths in Africa occur in Children <5y
- Whereas in areas with less transmission and low immunity: ALL age groups are at risk
- Local residents who leave high-transmission endemic areas for >6 months lose their immunity => NON-immune
- All NON-immune persons are highly vulnerable to symptomatic Malaria including SEVERE attacks
- While not considered "immunity" per se, Sickle Cell and Thalassemia genetic alterations significantly lower the risk of Malaria and its complications

INCUBATION PERIOD

- The incubation period in humans for most types of Malaria varies from 7–35 days
- Shorter periods (average 12–14 days) occur most frequently with *P. falciparum*

CLASSIC MALARIA PAROXYSM

- 3 stages of the "Classic Malaria Paroxysm"
  - (Primarily seen in Adults… but not until several days into the illness)
  - Symptoms last several hours include:
    - "Cold": shaking chills (with rigors… unlike Typhoid Fever)
    - "Hot": temperature ≥40°C (104°F), systemic symptoms, "dry," i.e., with minimal or no diaphoresis
    - "Sweating": diaphoresis and fatigue as the fever abates
- Typical fever patterns in Adults – with each episode lasting several hours:
  - Tertian (every 48 hrs): *P. falciparum*, *P. vivax, P. ovale*
    - Paroxysms occurring at regular intervals are more common with *P. vivax* or *P. ovale* than *P. falciparum*
  - Quartan (every 72 hrs): *P. malariae*
  - Because fever may lack periodicity early on…
    - Therefore, the absence of this feature does not rule out the possibility of Malaria
- With improvements in early diagnosis and treatment, these traditional cyclic fevers are seen less frequently

CLINICAL MANIFESTATIONS OF FALCIPARUM MALARIA

- Uncomplicated Falciparum Malaria
  - Symptomatic infection
    - Fever >38°C (>100.4°F) or history of fever within the past 48 hours
    - With or without other symptoms such as nausea & vomiting, diarrhea, headache, back pain, chills, myalgia…
    - Even abdominal pain and bronchitis!
  - In whom other obvious causes of fever have been excluded
  - ADULTS
    - Limited, nonspecific findings on Physical Exam:
      - Fever, tachycardia, tachypnea, ill appearance
      - Other findings – relate mostly to complications
        - E.g., Pallor (from hemolytic anemia)
    - Positive parasitemia <4% (if lab available)
    - Absence of Severe Malaria symptoms [see below]
  - CHILDREN
    - As noted, often do not have Classic Malaria Paroxysm pattern

- ✧ Prominent features in Children include:
  - ♦ Fever, generally quite high >40°C (>104°F)
  - ♦ General malaise, fatigue, listlessness
  - ♦ Gastrointestinal: nausea, vomiting, loose feces
  - ♦ Headache

❖ **Warning Signs of <u>More Serious</u> Malaria**

- ➢ CHILDREN – <u>Warning Signs</u>
  - ✧ Dehydration (if vomiting and loose feces are severe)
  - ✧ Pallor (from hemolytic anemia)
    - ♦ Frequently exacerbated by underlying nutritional deficiencies and intestinal geohelminth infection
  - ✧ Hepatosplenomegaly (may take days to appear)
  - ✧ Jaundice
  - ✧ Respiratory distress (Kussmaul's respirations) may indicate Lactic Acidosis due to Severe Malaria
  - ✧ Decreased Level of Consciousness or Seizures may be due to Hypoglycemia [or] Cerebral Malaria

❖ **Indications for Hospitalization** – because these patients may deteriorate rapidly:

- ➢ Young Children
- ➢ Immunocompromised patients
- ➢ Non-immune patients
- ➢ Hyperparasitemia (4–10%) but <u>no signs</u> of Severe infection <u>YET</u>

❖ **Definition of SEVERE Malaria** / Manifestations <u>at ANY age</u>:

- ➢ Symptoms like uncomplicated Malaria
- ➢ PLUS <u>parasitemia</u> >10% (>500,000/μL if lab available)
- ➢ PLUS, <u>prostration</u> associated with major signs of <u>organ dysfunction / failure</u> as evidenced by ≥1 of these:
  - ✧ Impaired consciousness
  - ✧ Multiple seizures
  - ✧ Hypoglycemia
  - ✧ Severe anemia (hemoglobin <7 g/dL)
  - ✧ Jaundice
  - ✧ Pulmonary edema (may include ARDS)
  - ✧ Significant bleeding / Coagulopathy or Disseminated Intravascular Coagulation
  - ✧ Acidosis (multifactorial)
  - ✧ Hemoglobinuria / Renal impairment ("Blackwater Fever")
  - ✧ Shock
- ➢ Increasing evidence supporting a "Cytokine Storm" in the pathogenesis of Severe Malaria
- ➢ The risk of death due to Severe Malaria is greatest in the first 24 hours after presentation

[SEE: PAGE 17 – DEFINITION OF SEVERE MALARIA]

<u>CEREBRAL MALARIA</u>

❖ Defined as: Encephalopathy presenting with impaired consciousness, delirium, and/or seizures

- ➢ Generally caused by *P. falciparum*
- ➢ Onset may be gradual or sudden
- ➢ Focal neurologic signs are unusual
- ➢ Severity depends on several factors
  - ✧ Virulence of the parasite
  - ✧ Host immune response
  - ✧ Time interval between onset of symptoms and initiation of therapy
- ➢ These patients require <u>hospitalization</u>

- ❖ Children are at much greater risk of developing Cerebral Malaria
- ❖ Prognosis
  - ➢ If untreated, Cerebral Malaria is almost 100% fatal
  - ➢ With treatment, mortality is 15–20%

SEQUELAE OF CEREBRAL MALARIA

- ❖ Adults: May cause permanent neurological sequelae in <3%
- ❖ Children: Are also at MUCH higher risk of adverse effects
  - ➢ E.g., ~50% of 20,000 Kenyan Children with Falciparum Malaria reportedly had neurologic involvement!
  - ➢ Persistent cognitive impairment
    - ✧ ~25% of Children even 2 years post episode
    - ✧ Primarily, attention and language problems
  - ➢ Significant residual neurologic deficits are also reported
    - ♦ E.g., Hemiplegia, Cerebral Palsy, Cortical Blindness, Deafness, Epilepsy

DIAGNOSTIC LABORATORY TESTS

- ❖ Microscopy
  - ➢ Thick smear – considered the "gold standard" for diagnosis
    - ✧ More likely to see parasites if >25 parasites/μL in expert hands
    - ✧ But labor-intensive, requiring ~40 minutes of Lab Tech time per specimen
      - ♦ Also requires ongoing training, certification, specific supplies, a well-maintained light microscope with 1000x oil immersion magnification, and electricity!
  - ➢ Thin smear: better for identifying species
- ❖ Rapid Diagnostic Tests ("RDTs")
  - ➢ Useful alternative if microscopy is not available
    - ✧ Results in 15–20 minutes
    - ✧ Limiting threshold for detection is >100–200 parasites/μL
    - ✧ With many different test kits available, as of 2018, the WHO established a "prequalification" program
      - ♦ A list of prequalified Malaria RDTs is maintained online
  - ➢ RDTs ONLY exist for *P. falciparum*; *P. falciparum* vs non-falciparum (not otherwise specified); [or] *P. falciparum* and *P. vivax*
    - ✧ Sensitivity/specificity: *P. falciparum* (>90%), *P. vivax* (>80%)
    - ✧ There are no reliable RDTs specifically designed to detect *P. malariae, P. ovale,* or *P. knowlesi*
  - ➢ Limitations:
    - ✧ Poor accuracy with untrained personnel
    - ✧ Inability to quantify level of parasitemia
    - ✧ False positives occur after recent successful treatment
    - ✧ **NEW ISSUE:** pfhrp2/3 gene deletions have become a clinically significant / expanding problem
      - ♦ These *P. falciparum* parasites are undetectable by HRP2-based RDTs => **false-negative RDTs!**
        - ○ With potentially lethal clinical consequences
      - ♦ Reported in >40 countries
        - ○ Requiring official RDT changes in South American and Horn of Africa
  - ➢ CDC recommends:
    - ✧ Positive [or] negative RDT: Should always be confirmed by microscopy, if possible…
- ❖ PCR testing: definitively identifies the species of Malaria parasite and detects mixed infections
  - ➢ But primarily remains a research tool
- ❖ Other Laboratory Findings:
  - ➢ Anemia (due to hemolysis) is seen in prolonged, severe, or recurrent disease
  - ➢ Mild leukopenia (3,000–6,000 WBC/μL)
    - ✧ IF Leukocytosis is present – consider an alternative diagnosis

- Thrombocytopenia – nonspecific since it may also be seen with other illnesses
- Hypoglycemia most often found in:
  - Young Children & Pregnant Women => poorer prognosis
  - Severe disease
  - Patients treated with Quinine (which induces hyperinsulinemia)
- Liver Transaminases are also often elevated

❖ "Hyperparasitemia" recently re-defined as:
- >2% of RBCs parasitized in low Malaria endemic areas
- >5% of RBCs parasitized in high Malaria endemic areas

DIFFERENTIAL DIAGNOSIS

❖ Malaria may mimic – or coexist with – other common diseases including:
- Typhoid / Enteric Fever
- Dengue and other Viral Infections
- Pneumonia
- Sepsis due to Bacteremia
- Meningitis… etc.

❖ Differentiating Cerebral Malaria versus Meningitis in Children
- Requires a lumbar puncture

MEDICINES FOR TREATING MALARIA

❖ Chloroquine or Hydroxychloroquine
❖ Two important currently used antimalarial drugs are derived from plants whose medicinal values had been noted for centuries:
- Artemisinin from the Qinghaosu plant (China, 4th century)
- Quinine from the Cinchona tree (South America, 17th century)

❖ Primaquine
❖ Mefloquine (Lariam®)
❖ Atovaquone/Proguanil (Malarone®)
❖ Sulfadoxine/Pyrimethamine (Fansidar®), also abbreviated "S/P"
❖ Amodiaquine (not available in the U.S.)

COUNTERFEIT ANTI-MALARIAL DRUGS

❖ There is an alarming prevalence of counterfeit antimalarial drugs (30–50%) in multiple countries across Southeast Asia
- Purchased in a range of different venues
  - Including informal shops, pharmacies, and even hospitals too!

❖ Africa also has increasing evidence of counterfeiting and poor-quality drugs
- Esp. those purchased outside the formal healthcare system

❖ This criminal behavior requires more attention

TREATMENT OF UNCOMPLICATED MALARIA

❖ **CHLOROQUINE**: First-line therapy in limited areas
- I.e., regions without known drug resistance including:
  - Caribbean: Haiti, Dominican Republic
  - Mexico
  - Central America: West (and north) of the Panama Canal zone
  - Middle East: Historically some areas of the Arabian Peninsula

- Orally as Chloroquine Phosphate Tablets or Suspension in divided doses over 3 days
  - Adults: Total cumulative dose of 1500 mg of "Base" (= 2500 mg of the "Salt" form)
  - Peds: Total cumulative dose of 25 mg/kg of Base (but never more than 1500 mg)
- Safe for use throughout pregnancy

❖ **HYDROXYCHLOROQUINE**
- Tablets are slightly different strength than Chloroquine
- Dosage schedule and regional limitations are the same

❖ **ARTEMISININ DERIVATIVES**
- First-line therapy in Chloroquine-Resistant regions (i.e., most of the world)
- Active against a broader life cycle range of blood stage parasites and gametocytes vis-à-vis Quinine
- Effective against MOST drug-resistant *P. falciparum*
- Wide variety of formulations available: oral, parenteral, and rectal
- Very well tolerated
- Preferred fixed-dose combination for oral therapy:
  - Artemisinin Combined Therapy ("ACT")
    - WHO primarily recommends:
      - Artemether–Lumefantrine ("AL") (taken after a high-fat meal)
        - **If >65 kg**, pharmacokinetic underdosing is a risk causing subtherapeutic blood levels
          - Efficacy reportedly drops to ~90% which may require 5-day dosing, closer follow-up, and consider switching to an alternative regimen, e.g., atovaquone-proguanil
        - AL accounts for ~85% of the public sector treatment market
          - Predictably, signs of reduced efficacy are emerging…requiring strategic diversification
      - Artesunate–Mefloquine ("ASMQ")
      - Artesunate–Amodiaquine ("AS+AQ") (not available in the U.S.)
    - Choice dependent on local resistance to the second agent
- Artemisinin derivative given ≥3 days but should not be used as monotherapy (risk of resistance)
- Also, they are not used for prophylaxis due to their short half-lives
- Pregnancy:
  - During the first trimester ACTs are an alternative treatment if Quinine + Clindamycin is not available
    - Due to the limited safety data for ACTs, they are considered a second-line choice

❖ Reducing Transmissibility with **PRIMAQUINE**
- Gametocytes may persist in the blood after successful treatment with ACT or Chloroquine
  - Serve as a source of ongoing transmission (via new mosquito bites)
  - WHO recommends Primaquine 0.25 mg/kg single dose on Day#1
    - Exception: Avoid for pregnant women and infants <6m
  - Studies in 2022 et seq.: G6PD testing is NOT required for this low-dose treatment protocol

❖ **TAFENOQUINE** (Krintafel™, Arakoda™)
- Was FDA-approved in 2018 for 2 indications:
  - Curative treatment for *P. vivax* Malaria
  - Malaria prophylaxis in non-pregnant individuals ≥16y
- Requires only a single dose, HOWEVER, requires G6PD testing before use

❖ **MEFLOQUINE** (Lariam®)
- Effective against Chloroquine- and S/P-resistant *P. falciparum* and *P. vivax*
- Side effects include neuropsychiatric problems, nausea, vomiting, diarrhea
- Contraindicated if 1st trimester of pregnancy, history of seizures, psychiatric issues (including depression), cardiac arrhythmias

- **ATOVAQUONE/PROGUANIL** (Malarone®)
  - Effective in Chloroquine-resistant *P. falciparum* and *P. vivax*
  - Excellent safety and tolerability but expensive and requires a fatty meal
  - Not approved in pregnancy
- **SULFADOXINE/PYRIMETHAMINE** (Fansidar®), also abbreviated "S/P"
  - Considered a less optimal choice
  - Used for suspected Chloroquine resistance
  - However, resistance of *P. falciparum* to S/P is reportedly increasing
  - Avoid in 1st trimester and last 2 weeks of pregnancy (due to its sulfa content)
- **IF POSSIBLE**: should not use the same or related drugs to treat a patient's episode of acute Malaria that had already recently been used for prophylaxis
- **QUININE SULFATE** (especially IV; but only PO formulation available in the U.S.)
  - Primarily reserved for resistant or Severe Malaria, becoming second-tier
    - Highly effective but not well tolerated
  - Typically used in combination with an antimalarial antibiotic (e.g., Doxycycline, Tetracycline, or Clindamycin)
  - Side effects / Risks include:
    - Cinchonism (tinnitus, hearing loss, nausea, vomiting)
    - Hypoglycemia (induces hyperinsulinism esp. Infants and Pregnant Women)
      - Therefore, must administer in D10W = 10% Dextrose in Water)
    - Cardiac arrhythmias
  - Safe with pregnancy during the 1st trimester, esp. Quinine + Clindamycin for 7 days
- In the U.S.: Currently, Malaria treatment regimens available with a reliable supply include:
  - Artesunate IV
    - 2020: FDA-Approved
    - 2024: CDC guidelines were updated: use in Severe Malaria regardless of the Plasmodium species
  - Artemether–Lumefantrine – preferred follow-on oral treatment (but if >65kg…see above)
  - Atovaquone–Proguanil
- Monitoring and Follow-Up
  - With appropriate treatment, fever and parasitemia usually resolve within 2–4 days
  - Please Note: Dosages of these medications are not included in this presentation but are readily available at UpToDate® or the WHO publication which was updated in August 2025 [SEE: Reference #4 (below)]

TREATMENT OF SEVERE MALARIA

- Severe Malaria is a medical emergency and should be treated urgently and aggressively
- Best provided in an Intensive Care Unit (ICU) with careful clinical monitoring including:
  - Glucose levels, hematocrit, level of consciousness, quantification of parasitemia (used for detecting early drug resistance)
- Parenteral antimalarials are preferred (i.e., intravenous or intramuscular)
  - WHO treatment of choice: Artemisinin derivatives parenterally, especially Artesunate (vis-à-vis Quinine)
    - This is the preferred treatment for Severe Falciparum Malaria in ALL Adults and Children (including Infants, Pregnant Women in all trimesters, and Lactating Women)
  - Give parenteral antimalarials (Artimisinin derivatives or – if outside the U.S. – Quinine) for minimum of 24 hours (irrespective of the patient's ability to tolerate oral medications earlier)
  - Thereafter, administer a complete treatment course of oral ACT (Artemisinin Combined Therapy)
  - In Pregnancy
    - Parenteral Artesunate [or] IM Artemether
    - Alternative option: Parenteral Quinine (used outside the U.S. – is administered ONLY until Artesunate can be obtained)

- Exchange transfusions are explicitly no longer recommended in the CDC's 2024 guidelines
- FYI: PRE-Referral intramuscular Artemisinin derivatives can potentially be life-saving in Severe Malaria in Adults
  - However, single-dose artesunate rectal suppository ONLY reduces mortality in Children <6y
    - Low-quality evidence advises against using suppository treatments for older Children and Adults

RESISTANCE OF *P. FALCIPARUM*

- Resistance: defined as persistent parasitemia despite ≥3 days of proper antimalarial therapy and compliance
- **Chloroquine** resistance
  - As noted, is common in most endemic areas worldwide
- **Artemisinin *Partial* Resistance** (ART-R) mediated primarily by PfKelch13 mutations
  - Has been confirmed in the WHO's World Malaria Report 2025 in East Africa
    - Including Tanzania, Uganda, Rwanda, and Eritrea
    - Suspected resistance also in Ethiopia, Sudan, Zambia, and Namibia
  - However, almost all patients treated with ACT recover if the partner drug remains efficacious in the region
- **Mefloquine** resistance may overlap with Quinine resistance
  - Areas of Southeast Asia and Africa
- **Atovaquone-Proguanil** resistance – only occasionally reported
- **Clinical Parameters**
  - A patient who has not improved clinically and defervesced within 72 hours may have an ART-R strain
    - If possible, in Resource-Limited Areas, a follow-up blood smear should be ordered
    - And consider other factors, e.g., inadequate adherence, inadequate drug doses, counterfeit drugs, etc.
- **Encouraging News**:
  - Recent successes against serious ART-R in the Greater Mekong Subregion have been noteworthy
    - Proving that aggressive elimination strategies combined with robust surveillance and flexible treatment policies can effectively contain even severe multidrug resistance
  - In 2020, researchers reported an entirely new compound class for treating Malaria
    - Labeled the Imidazolopiperazines (IZP) class
    - In late 2025, Ganaplacide-Lumefantrine (GanLum – Novartis) achieved positive Phase 3 status
      - First non-artemisinin-based antimalarial in 25 years
      - Effective against drug-resistant parasites and blocks transmission
      - Submission to regulatory authorities for approval and licensing is expected in 2026

TREATMENT OF NON-FALCIPARUM MALARIA

- **Chloroquine**: Is the preferred first-line agent for non-falciparum Malaria in MOST areas
  - However, Chloroquine resistance has been reported in *P. vivax* infections
    - Esp. found in Oceania and Indonesia (>30%), and a lesser degree in most *P. vivax*-endemic countries
  - Therefore, use ACT with Piperaquine, Lumefantrine, or Mefloquine in these locations
- *P. vivax* and *P. ovale* : Need to ADD full-dose **Primaquine**
  - Used to eradicate these parasites (hypnozoites) from the liver
  - But only use if able to test for G6PD Deficiency – due to the risk of severe hemolysis reaction
  - Never prescribe for Pregnant Women (cannot test the fetus for G6PD Deficiency)
- RECENTLY: Point-of-care G6PD spot test exists for rapid (<5 min.) diagnosis from a fingerstick blood sample
  - A quantitative POC test, Biosensor, was prequalified by the WHO in 2024 for screening patients
- Patients with Severe Malaria should be treated for presumed *P. falciparum*, **regardless** of the causative species

PREVENTION – PUBLIC HEALTH

- WHO: Vector control is the primary method of reducing and preventing Malaria transmission
  - WHO: Progress in global Malaria control is threatened by emerging resistance to insecticides among *Anopheles* mosquitoes

- ✧ In 2020: 78 countries reported mosquito resistance to at least 1 of the 4 commonly-used insecticide classes during the period 2010–2019
- ✧ In 29 countries, mosquito resistance was reported to ALL main insecticide classes

➢ **3 Forms of <u>Vector Control</u>**: 2 current and 1 for the future:

- ✧ Indoor residual spraying **(IRS)** with effective insecticides
  - ♦ Rapidly reduces Malaria transmission
  - ♦ Reaches its full potential when >80% of houses are sprayed
  - ♦ Remains effective for 3–6 months
- ✧ Long-Lasting Insecticidal Nets **(LLINs)**
  - ♦ These are the preferred insecticide-treated mosquito nets (ITNs) for public health
  - ♦ Netting is impregnated with pyrethroids, <u>etc.</u> during manufacturing
  - ♦ Pyrethroids generally kill any mosquito that comes in contact
    - ○ However, Pyrethroid <u>resistance</u> is now surging in some sub-Saharan African countries
      - ★ WHO guidelines of 2024 recommend Pyrethroid-PBO (piperonyl butoxide)-treated bednets
      - ★ Next-generation options include pyrethroid-chlorfenapyr and pyrethroid-pyriproxyfen
      - ★ The choice is guided by local resistance profiles
  - ♦ Unfortunately, in some countries, LLINs are almost impossible to obtain
    - ○ Recognizing that untreated bednets are <u>not</u> generally approved nor effective protection against Malaria!
  - ♦ Of pertinence, the latest WHO guidelines for Malaria 2025, recommend against co-deployment of LLINs in conjunction with IRS; priority should be given to optimizing coverage of one or the other
  - ♦ **<u>Proper Care of LLINs</u>** – A valuable teaching opportunity for patients and the community:
    - ○ Only wash with soap 3 times annually; otherwise simply shake out dust
    - ○ Avoid using "iron soap" (commonly found in Africa)
    - ○ Never hang in the sunlight to dry
    - ○ Promptly repair any rips or tears in the material
    - ○ Carefully tuck the bottom edges under the mattress or mat for both naps and overnight
    - ○ <u>Especially</u> important protection for the "most vulnerable" persons:
      - ★ I.e., Children <5y and Pregnant Women
    - ○ Field studies show this Care Protocol for LLINs allows <u>~3 years</u> of effective protection
- ✧ **Genetic Engineering** for Control – Future
  - ♦ Entails using male mosquitoes to introduce genetic factors that
    - ○ Prevent the eggs from hatching, or
    - ○ Prevent larvae from surviving, or
    - ○ Produce adult insects incapable of transmitting human disease
  - ♦ Despite years of investigation, the optimal approach for selectively incorporating genetic factors into later generations in a wild population is under intense study…but <u>remains uncertain</u>

<u>PREVENTION – PROPHYLACTIC TREATMENT</u>

❖ Intermittent Preventive Treatment **(IPT)** <u>in-country</u>

- ➢ Appears to be useful for reducing the risk of Malaria infections among high-risk individuals
  - ✧ Esp. Pregnant Women

❖ IPT and seasonal prophylaxis of target groups are important policies of the WHO's Strategic Plan

❖ Monoclonal antibodies – novel approach published in *NEJM* in 2022

- ➢ May be useful where there is antimalarial resistance or for immunocompromised individuals

PREVENTION – TRAVELERS AND VOLUNTEERS

- Chemoprophylaxis
  - Mefloquine (Lariam®) weekly – usually for trips of >4 weeks
  - Atovaquone-Proguanil (Malarone®) daily – usually for trips of <4 weeks
  - Doxycycline daily (only for those >8y)
  - If Chloroquine-sensitive region: Chloroquine weekly
- For maximum benefit, prophylaxis must be combined with the use of "personal protective measures"
  - E.g., long sleeves, long pants, socks, and then sleeping in a mosquito-free setting or using LLINs
  - Repellants with DEET 30–50% [or] Picaridin 20% (both are safe in pregnancy & breast-feeding)
    - DEET is preferred for maximal protection against mosquitoes
  - Permethrin or other insecticides pre-treated or sprayed onto clothing (never applied onto skin)
- Travelers to malarious areas must understand:
  - Compliance with these prophylactic measures is essential
  - However, NO chemoprophylaxis/personal protective regimen guarantees 100% protection
  - Be advised: Fever during or after travel to a malarious area is a medical emergency requiring urgent medical attention
- As noted in the Epidemiology section (above), locally acquired Malaria cases have been reported in the U.S.
  - Thus, local transmission, i.e., without international travel, is possible under the right conditions

PREVENTION – VACCINES

- WHO: In 2021 recommended broad use of RTS,S/AS01 a.k.a. **"RTS,S"**
  - Vaccine against Falciparum Malaria
  - FINALLY approved, after 30 YEARS of research and development by GSK and their collaborative partners
  - This is the FIRST-EVER vaccine approved against ANY parasite in the history of the world!
  - Acts against *P. falciparum* – the deadliest strain and the most prevalent in Africa
    - Esp. useful among African Children living in regions with moderate-high *P. falciparum* transmission
    - Given as a 4-dose schedule for Children starting at 5 months of age
  - Studies of >800,000 Children since 2019 with 2.3 Million doses administered in 3 African countries
    - Safety profile has been favorable
    - But only 30% reduction of Severe/deadly Falciparum Malaria
  - Combining this vaccine with chemoprevention substantially enhanced disease reduction compared to either intervention alone
  - Positive impact even further enhanced when implemented side-by-side with other preventive measures (LLINs, etc.)
- A second vaccine, R21/Matrix-M a.k.a. **"R21"**
  - A 3-dose series with a 4th dose a year later
  - Reporting >75%(!) reduction of symptomatic cases of Falciparum Malaria in Young Children in both seasonal and perennial Malaria transmission areas
  - WHO recommended and prequalified this product in 2023
  - Now deployed in 17 African countries incorporating this into their routine childhood immunization programs
- Other Malaria vaccines, such as *Plasmodium falciparum* sporozoites (PfSPZ) and several derivatives, are also under development but present new hurdles such as requiring administration via direct venous inoculation
- And finally, mRNA-based vaccine strategies are also under investigation

REASONS TO EXPECT IMPROVING FUTURE TRENDS

- Factors that can contribute toward reducing the prevalence of Malaria:
  - More sensitive diagnostic tools
  - Effective use of antimalarial drugs
  - Improved personal and community protection
  - Better vector (mosquito) control
  - Deployment of new Malaria vaccine(s)

PROGRESS TO ELIMINATION

- Because there are no non-human reservoirs for the human Plasmodia
  - Malaria is considered to be a candidate for global eradication
- Efforts towards elimination are continually expanding worldwide
  - Countries reporting zero indigenous cases are increasing
    - E.g., from 2010 to 2025: the initial report of 15 countries has now increased to 47 countries and one territory as having been officially WHO-certified as Malaria-free!

INFORMATION RESOURCES

1) Excellent country-by-country information about Malaria from the International Association for Medical Assistance to Travelers (IAMAT)

   www.iamat.org/risks/malaria

2) Malaria information and prophylaxis for Healthcare Professionals, by country

   www.cdc.gov/yellow-book/hcp/preparing-international-travelers/yellow-fever-vaccine-and-malaria-prevention-information-by-country.html

3) Current WHO Global Malaria Programs towards prevention and eradication

   www.who.int/health-topics/malaria#tab=tab_1

4) Link to a user-friendly WHO online platform: ***WHO Guidelines for Malaria 2025*** (in English)

   www.who.int/publications/i/item/guidelines-for-malaria

5) Frequently updated information on diseases across the globe from the CDC country-by-country

   wwwnc.cdc.gov/travel/destinations/list

   SEE: "Clinician Resources" (on the left side column)

   SEE: (also on the left column): Advice for Travelers / Humanitarian Aid Workers (listed alphabetically on a long list of topics)

6) CDC Malaria Hotline:

   Monday–Friday, 9AM–5PM Eastern time: 770-488-7788

   After hours: 770-488-7100 (ask to speak to the Malaria clinician on call)

7) UpToDate® ©2026 – Licensed by subscription to Duane R Spaulding MD

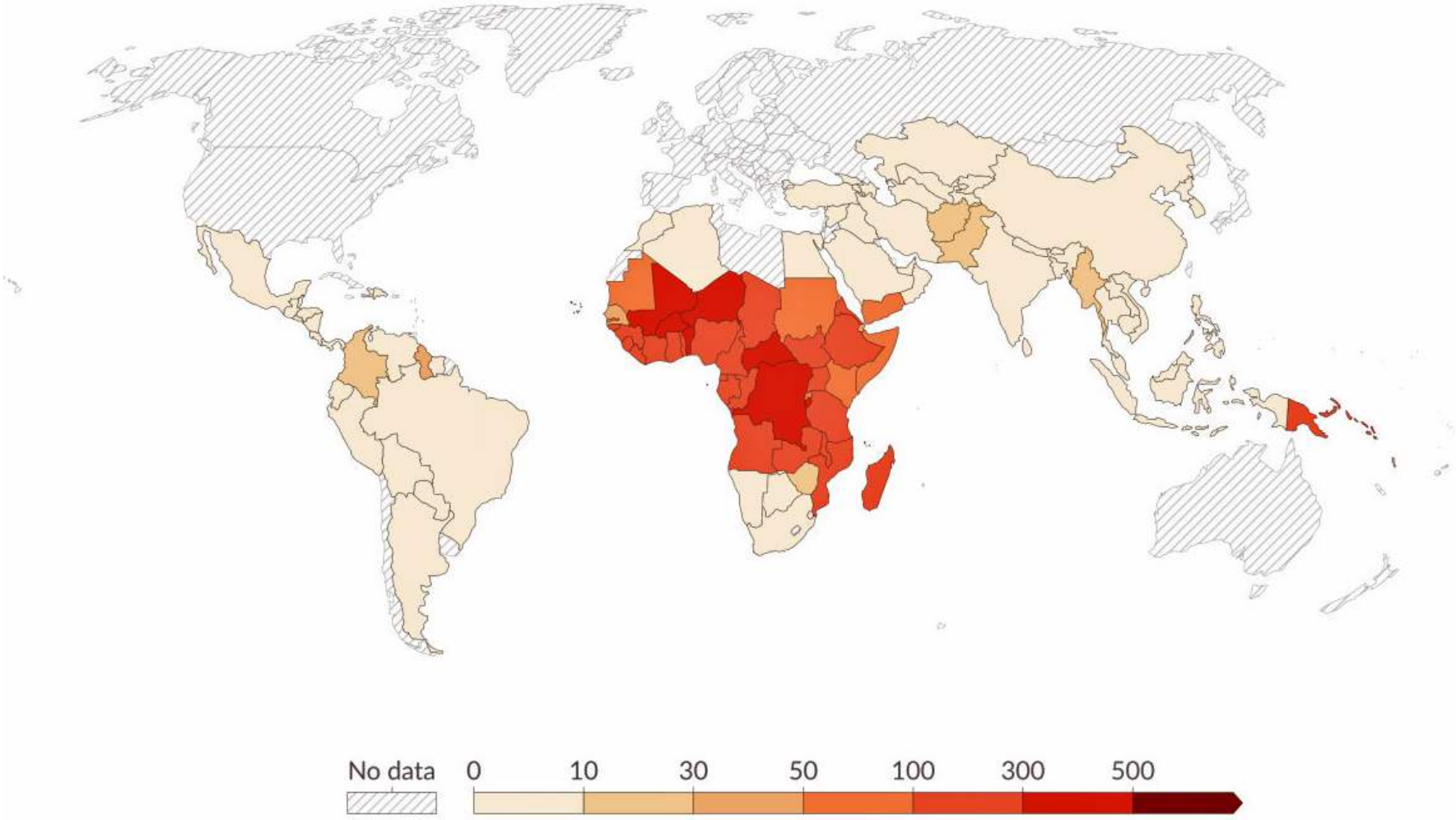
   www.uptodate.com

THANK YOU!

New cases of malaria per 1,000 people at risk, 2024

Our World in Data

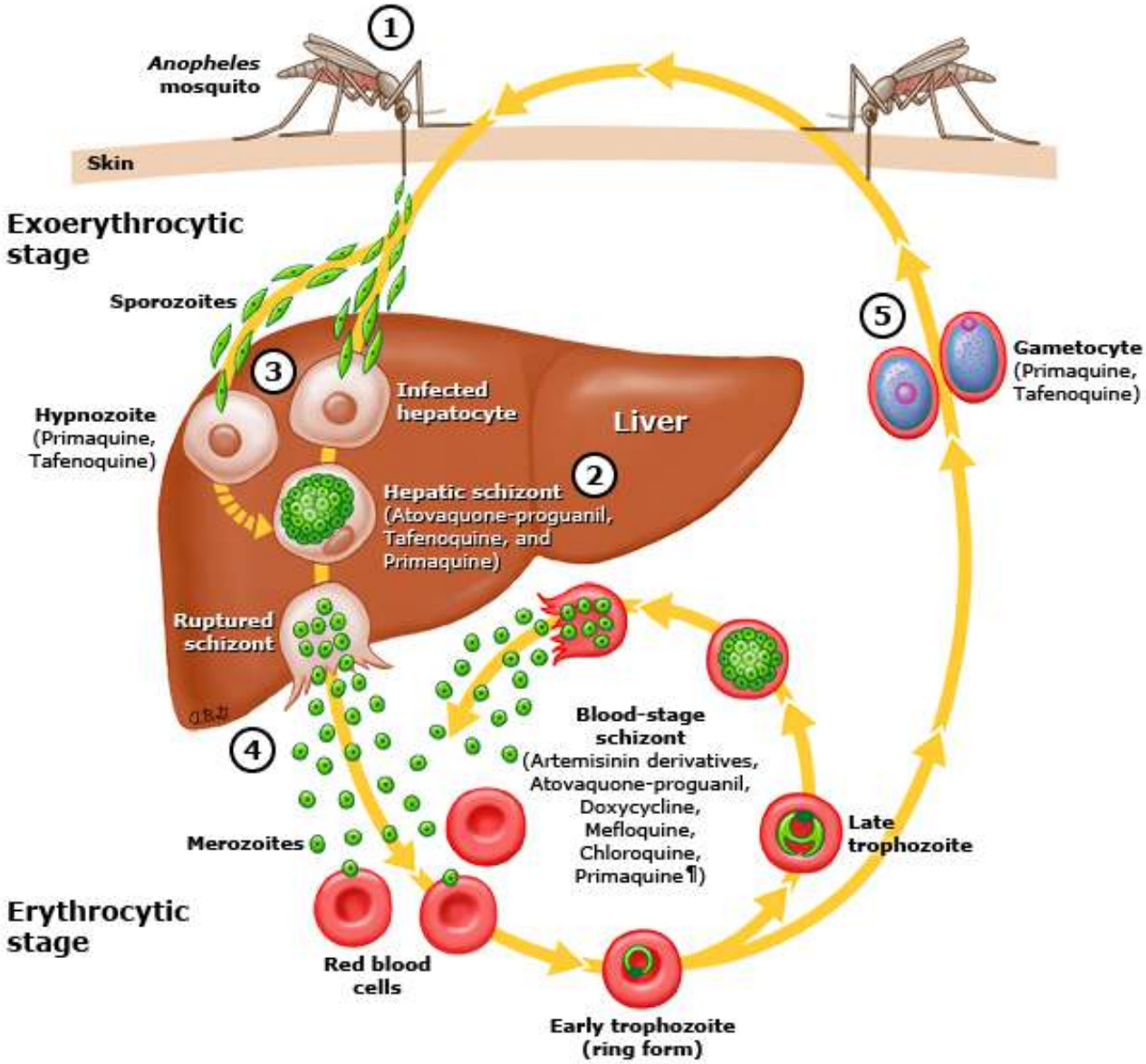
Malaria[1] is a life-threatening disease caused by parasites that are transmitted by certain types of mosquitoes.



Data source: World Health Organization (Global Health Observatory), via World Bank (2026)

OurWorldinData.org/malaria | CC BY

Life cycle of *Plasmodium**



(1) *Plasmodium*-infected *Anopheles* mosquito bites a human and transmits sporozoites into the bloodstream.

(2) Sporozoites migrate through the blood to the liver where they invade hepatocytes and divide to form multinucleated schizonts (pre-erythrocytic stage). Atovaquone-proguanil, tafenoquine, and primaquine have activity against hepatic-stage schizonts.

(3) Hypnozoites are a quiescent stage in the liver that exist only in the setting of *P. vivax* and *P. ovale* infection. This liver stage does not cause clinical symptoms, but with reactivation and release into the circulation, late-onset or relapsed disease can occur up to many months after initial infection. Primaquine and tafenoquine are active against the quiescent hypnozoites of *P. vivax* and *P. ovale*.

(4) The schizonts rupture and release merozoites into the circulation where they invade red blood cells. Within red cells, merozoites mature from ring forms to trophozoites to multinucleated schizonts (erythrocytic stage). Blood-stage schizonticides such as artemisinins, atovaquone-proguanil, doxycycline, mefloquine, tafenoquine, and chloroquine interrupt schizogony within red cells.

(5) Some merozoites differentiate into male or female gametocytes. These cells are ingested by the *Anopheles* mosquito and mature in the midgut, where sporozoites develop and migrate to the salivary glands of the mosquito. The mosquito completes the cycle of transmission by biting another host.

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* There is strong evidence that drugs listed in parentheses are active against designated stage of parasitic life cycle.

¶ Primaquine is a blood-stage schizonticide with activity against schizonts of *P. vivax* but not those of *P. falciparum*.

Graphic 70176 Version 10.0

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.
Hypoglycemia	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 anemia	Hemoglobin 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: ▪ *Plasmodium falciparum* parasite count >2.5% parasitemia ▪ *Plasmodium knowlesi* 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 crepitations 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).
Hyperparasitemia	*P. falciparum*: ▪ In non-immune travelers: parasitemia ≥5%[1] ▪ All patients: parasitemia >10% *P. knowlesi*: ▪ Parasite density >100,000 parasites/uL ▪ Jaundice and parasitemia >15,000 parasites/microL *Plasmodium vivax*: ▪ No established parasite density thresholds

Severe malaria is defined as one or more of the above criteria, occurring in the presence of malaria infection and in the absence of an identified alternative cause.